Neuropsychological Assessment in The Edinburgh High Risk for Schizophrenia Study

Majella M. Byrne

PhD degree
Submitted to The University of Edinburgh, May, 2000.

Table of Contents

TABLE OF CONTENTS: TABLES 7
TABLE OF FIGURES 10
ACKNOWLEDGEMENTS 11
DECLARATION OF AUTHORSHIP 12
ABSTRACT 13
SUMMARY OF THE ORGANISATION OF THE THESIS 14
RELEVANT PUBLICATIONS BASED ON DATA THAT APPEARS IN THIS THESIS 15

CHAPTER ONE: AETIOLOGICAL THEORIES OF SCHIZOPHRENIA AND HIGH-RISK RESEARCH 17

1.1.OVERVIEW OF SCHIZOPHRENIA 18
1.2 BACKGROUND AND DIAGNOSIS 18
1.3 EPIDEMIOLOGY 19
1.4. AETIOLOGICAL THEORIES 22
1.4.1 Genetics 22
1.4.1.1 Segregation analysis 26
1.4.1.2. Linkage studies 27
1.4.2. Neurodevelopmental theories of the origin of schizophrenia: 28
1.4.2.1 Overview of neurodevelopmental theories 28
1.4.2.2. Precursors of schizophrenia 29
1.4.2.3. Neuro-imaging 30
1.4.2.4. Neuropathology 31
1.4.2.5. Obstetric complications 32
1.4.2.6. Season of birth 34
1.4.2.7. Viral infection hypothesis 35
1.4.2.8. Minor physical anomalies 37
1.4.2.9. Dermatoglyphics 38
1.4.2.10 Handedness 39
1.4.3. Research on neurotransmission 39
1.4.4. Sociological explanations 40
1.4.5. Family environment 41
1.4.6. Conclusion 42
1.6. HIGH-RISK STUDIES OF SCHIZOPHRENIA 43
1.6.1.High-risk (HR) studies 43
1.6.2. The high-risk paradigm; problems, limitations, and necessary considerations 44
1.6.3. Goals for HR research 47
1.6.4. Issue of biological heterogeneity 49
1.6.5. Ethical issues 49
1.7. THE FIRST GENERATION HIGH-RISK STUDIES 50
1.7.1 General Review of High Risk studies 59
1.7.1.1. Summary of the review of HR studies 60
1.8. SUMMARY OF THE HIGH RISK LITERATURE 72
1.9 BIBLIOGRAPHY OF HIGH-RISK STUDIES 72

CHAPTER TWO: THE EDINBURGH HIGH RISK PROJECT 79

2.1. THE EDINBURGH HIGH RISK PROJECT: DESCRIPTION, AND METHODOLOGY. 80
The overall aims of the study 80
2.2. RECRUITMENT 82
2.3. PARTICIPANTS 82
2.3.1. High Risk Subjects 83
2.3.2. Controls subjects 85
2.3.3. First episode cases 86
2.4. SUBJECT ASSESSMENTS: BASELINE 89
2.4.1. Neuropsychological assessments 89
2.4.2. Clinical assessments 89

2.4.3. Social, Demographic Information *90*
2.4.4. Obstetric information *90*
2.4.5. Dermatoglyphics *90*
2.4.6. Brain imaging *90*
2.5. SUBJECT ASSESSMENT: FOLLOW-UP 91
2.5.1. Second Round Assessments *91*
2.5.2. Third Round Assessments *91*
2.6. COMPARISON OF THE GROUPS WITH RESPECT TO SOCIO-DEMOGRAPHIC CHARACTERISTICS 91
2.6.1. Social Class at origin *92*
2.6.2 Educational qualifications *93*
2.6.3. Education and employment status in the groups *94*
2.6.4. Outline of family history *95*
2.6.5. Age of subjects, gender, marital status and number of children *96*
2.6.6. Learning difficulties (reading, writing, and speech problems) *97*
2.6.7. Other school problems *98*
2.6.8. History of psychological difficulties *98*
2.6.9. Forensic history *99*
2.6.10 Social work involvement and appearance before the children's panel *100*
2.6.11. Alcohol consumption *101*
2.6.12. Current and past drug usage; cannabis *102*
2.6.13 Present State Examination ratings at each assessment *103*
2.6.14. Comparison of those who returned for the second round of assessments among the control and high-risk group and those who did not *106*

CHAPTER THREE: METHODOLOGY OF THE NEUROPSYCHOLOGICAL ASSESSMENTS 107

3.1. NEUROPSYCHOLOGICAL ASSESSMENT BATTERY 108
3.2. CURRENT AND PREMORBID COGNITIVE FUNCTIONING 111
3.2.1. The Wechsler Adult Intelligence Scale-Revised *111*
3.2.1.1. Data generated: WAIS-R 113
3.2.2. Block Design *113*
3.2.2.1. Data generated for analysis: Block design 114
3.2.3. The Speed And Capacity Of Language Processing Test *114*
3.2.3.1. Data generated: Speed And Capacity Of Language Processing Test 116
3.2.4. The National Adult Reading Test (NART) *116*
3.2.4.1. Data generated: NART 117
3.2.5. The Schonell Graded Word Reading Test *117*
3.2.5.1. Data generated: Schonell Graded Word Reading Test 117
3.3. EXECUTIVE FUNCTION 117
3.3.1. Hayling Sentence Completion Test *117*
3.3.1.1. Data generated: Hayling Sentence Completion Test 118
3.3.2. Stroop Colour Word Test *118*
3.3.2.1. Data generated: Stroop Colour Word Test 119
3.3.3. Verbal Fluency *119*
3.3.3.1. Data generated: Verbal Fluency 120
3.3.4. Trails Making Test A & B *120*
3.3.4.1. Data generated: Trails Making Test A & B 121
3.4. PERCEPTUAL MOTOR SPEED 121
3.4.1. Digit Symbol *121*
3.4.1.1. Data generated: Digit Symbol 122
3.5. MENTAL CONTROL/ENCODING 122
3.5.1. Digit Span *122*
3.5.1.1. Digits Forwards: 122
3.5.1.2. Digits Backwards: 123
3.5.1.3. Data generated for analysis: Digits forwards and Digits backwards 123
3.5.2. Arithmetic *123*
3.5.2.1. Data generated: Arithmetic 124
3.6. SUSTAINED ATTENTION 124

3.6.1. Continuous Performance Test -Identical Pairs *124*
3.6.1.1. Data generated: CPT-IP 129
3.7. VERBAL ABILITY AND LANGUAGE 130
3.7.1. Token Test *130*
3.7.1.1.Data generated: Token Test 131
3.7.2. Vocabulary *131*
3.7.2.1. Data generated: vocabulary 132
3.8. LEARNING AND MEMORY 132
3.8.1. Rivermead Behavioural Memory Test *132*
3.8.1.1. Data generated: Rivermead Behavioural Memory Test 132
3.8.2. Rey Auditory Verbal Learning Test and parallel versions *132*
3.8.2.1. Data generated: Auditory Verbal Learning Test 134
3.8.3. Visual Reproductions *134*
3.8.3.1. Data generated: Visual Reproductions 135
3.9. LATERAL PREFERENCES 135
3.9.1. Hand Preferences *135*
3.9.1.1. Data generated: Handedness measures 135
3.9.2. Foot and eye preference *136*
3.9.2.1. Data generated: Foot and eye preference 137

CHAPTER FOUR: EXPLORATORY DATA ANALYSIS 139

4.1.EXPLORATORY DATA ANALYSIS 140
4.1.1. Neuropsychological test results (excluding the CPT) *140*
4.2. METHODS OF DATA ANALYSIS 141
4.3. STEP 1: ASSESSING NORMALITY 142
4.4. STEP 2: PREPARATION FOR FACTOR ANALYSIS 147
4.5. STEP 3: STANDARDISING THE TEST SCORES 149
4.6. ANALYSIS OF THE CPT-IP 152

CHAPTER FIVE: NEUROPSYCHOLOGICAL ASSESSMENT OF YOUNG PEOPLE AT HIGH GENETIC RISK FOR SCHIZOPHRENIA, COMPARED TO CONTROLS AND PATIENTS WITH A FIRST EPISODE OF SCHIZOPHRENIA: BASELINE ANALYSIS ...153

5.1 NEUROPSYCHOLOGY AND SCHIZOPHRENIA: A SUMMARY OF THE LITERATURE 154
5.1.1. Background *154*
5.1.2.THE PROFILE OF NEUROPSYCHOLOGICAL IMPAIRMENT 155
5.1.2.1 Memory and schizophrenia 156
5.1.2.2 IQ in Schizophrenia 159
5.1.3. When do the deficits arise, and do they progress? *160*
5.1.4. Through what mechanisms do these deficits arise? *163*
5.1.5. How do the deficits relate to symptoms? *164*
5.1.6. The Continuous Performance Test *166*
5.1.7. Medication effects *169*
5.1.8. Neuropsychological investigations in HR and family studies *170*
5.1.8.1. IQ in high-risk subjects 170
5.1.8.2. Findings from the HR studies and studies of adult relatives of patients with schizophrenia. 172
5.1.8.3. Further Studies of Adult Relatives of patients with schizophrenia 175
5.1.9. Methodological considerations *176*
5.1.10. Summary of the evidence for neuropsychological impairment *177*
5.2. NEUROPSYCHOLOGICAL FUNCTIONING IN SUBJECTS FROM THE EDINBURGH HIGH RISK FOR SCHIZOPHRENIA STUDY: BASELINE ASSESSMENT 178
5.3. STATISTICAL ANALYSES 179
5.4. BASELINE UNADJUSTED ANALYSIS 179
5.4.1. Current Intellectual Function *179*
5.4.2. Pre-morbid Intellectual Function *180*
5.4.3. Executive Function *183*
5.4.4. Perceptual Motor Speed *184*
5.4.5. Mental control/ encoding *184*

5.4.6. Verbal ability and Language *184*
5.4.7. Learning and Memory *184*
5.4.8.Continuous Performance Test; initial analysis *186*
5.4.8.1. Distraction conditions 189
5.4.8.2. Speed conditions 189
5.4.9. Summary of univariate unadjusted analyses *191*
5.5. Analysis of data from the neuropsychological assessment battery; Controlling for premorbid intellectual function (NART) *192*
5.5.1. Executive function *193*
5.5.2. Perceptual Motor Speed *194*
5.5.3. Mental Control Encoding *194*
5.5.4. Verbal ability and Language *194*
5.5.5.Learning and Memory *195*
5.5.6. General Mental Ability *195*
5.5.7. CPT-IP analyses controlling for NART *199*
5.5.7.1. Distraction conditions 199
5.5.7.2. Speed conditions 199
5.5.8. Summary of univariate analyses controlling for NART *203*
5.6. MULTIVARIATE ANALYSIS 203
5.6.1. FACTOR ANALYSIS *204*
5.6.1.1. Interpretation of the factor analysis 205
5.6.1.2. Analysis of the factor scores 209
5.6.1.3.Summary of unadjusted analyses of factor scores 211
5.6.1.4. Summary of analyses of factor scores adjusting for the NART 211
5.6.2. Composite standardised Z scores *211*
5.6.2.1. Composite scores analysed without NART as a covariate 212
5.6.2.2. Composite scores analysed with NART as a covariate 213
5.6.2.3.Summary of the analyses of unadjusted composite scores 215
5.6.2.4. Summary of the analyses of composite scores controlling for NART 215
5.6.2.5. CPT-IP Standardised Z-scores 215
5.6.2.6.Summary of unadjusted CPT-IP composite score analysis 216
5.6.2.7. Summary of CPT-IP composite score analysis adjusting for NART 216
5.7. GENERAL SUMMARY OF CHAPTER FIVE 219
5.8. DISCUSSION 220

CHAPTER SIX: NEUROPSYCHOLOGICAL FOLLOW-UP OF YOUNG PEOPLE AT HIGH GENETIC RISK FOR SCHIZOPHRENIA COMPARED TO CONTROLS 227

6.1. INTRODUCTION 228
6.2. INITIAL FOLLOW-UP: FIRST TO SECOND ROUND ASSESSMENT 228
6.3.Statistical Analysis *228*
6.4. NEUROPSYCHOLOGICAL DIFFERENCES BETWEEN THOSE WHO ATTENDED FOR FOLLOW-UP AND THOSE WHO DID NOT. 230
6.5. RESULTS 231
6.5.1.Executive function *231*
6.5.2.Perceptual motor speed. *232*
6.5.3.Mental control encoding *232*
6.5.4.Verbal ability and language *232*
6.5.5.Learning and memory measures. *232*
6.5.6.Summary *234*
6.6. CPT-IP RESULTS 234
6.7. FOLLOW UP ASSESSMENTS: ASSESSMENTS 1,2 AND 3 241
6.8. DISCUSSION 247

CHAPTER SEVEN: THE ASSESSMENT OF HAND PREFERENCE IN THE GROUPS 253

7.1. LATERALISATION 254
7.2. LATERAL PREFERENCE MEASUREMENT 254
7.3. THEORIES OF HANDEDNESS 255
7.3.1. Birth stress hypothesis *255*

7.3.2. Prenatal and neonatal indicators of left handedness *256*
7.3.3. Neuropathological theories of left handedness *257*
7.3.4. Genetic theories of handedness *259*
7.3.5. The Annett theory of handedness *260*
7.4. CRITIQUE OF METHODS IN LATERALISATION RESEARCH 262
7.5. HANDEDNESS IN PATIENTS WITH SCHIZOPHRENIA: WHY IS IT IMPORTANT 263
7.6. CORRELATES OF NON-RIGHT HANDEDNESS IN SCHIZOPHRENIA 266
7.7. EYE PREFERENCES IN SCHIZOPHRENIA COMPARED TO CONTROLS 267
7.8. CONCLUSIONS 267
7.9. THE AIMS OF THE CURRENT STUDY: 268
7.10. METHOD 269
7.10.1. Hand Preferences *269*
7.10.1.1. Edinburgh Handedness Inventory 270
7.10.1.2. Annett Handedness Scale (1970) 270
7.10.2. Statistical analysis *271*
7.11. RESULTS 272
7.11.1. Round one; baseline assessment *272*
7.11.2 Annett classification system *286*
7.11.4.Relationship between handedness and socio-demographic variables *291*
7.11.4.1. Quantitative analysis 291
7.11.4.2. Qualitative analysis 292
7.11.5. Symptoms within the high-risk group and hand preferences *293*
7.11.6. The relationship between psychotic symptoms and eye and foot preferences within the high-risk group *294*
7.11.7. Incongruous hand/eye dominance *294*
7.12. DISCUSSION 294

CHAPTER EIGHT: NEUROPSYCHOLOGICAL ASSESSMENT RESULTS AND PSE SYMPTOMS 303

8.1. ORGANISATION OF CHAPTER EIGHT 304
8.2. BASELINE NEUROPSYCHOLOGICAL ASSESSMENT DATA ANALYSED BY SYMPTOMS. 305
8.2.1 Univariate analysis *305*
8.2.2. Symptoms by Factor Scores; baseline data *309*
8.2.3. Composite standardised Z scores; baseline data *309*
8.2.4.Continuous performance test and symptoms *310*
8.2.5 Effect of the presence of symptoms on the baseline analyses *310*
8.3. NEUROPSYCHOLOGICAL CHANGE AND PSYCHOTIC SYMPTOMATOLOGY 317
8.4. SYMPTOM CHANGE AND NEUROPSYCHOLOGICAL PERFORMANCE (ROUND 1 TO ROUND 2). 324
8.4.1. Summary of neuropsychological findings *327*
8.5. BREAKDOWN OF THE SOCIO-DEMOGRAPHIC VARIABLES BY SYMPTOMS (EVER RATED) 328
8.8.DISCUSSION 330

CHAPTER NINE: NEUROPSYCHOLOGICAL ASSESSMENT RESULTS, PSE SYMPTOMS, AND SOCIO-DEMOGRAPHIC DETAILS, ACCORDING TO FAMILY HISTORY OF PSYCHOSIS 335

9.1. INTRODUCTION 336
9.2. CATEGORICAL DEFINITION OF FAMILY HISTORY OF PSYCHOSIS 336
9.3. STATISTICAL ANALYSES OF THE NEUROPSYCHOLOGICAL DATA 339
9.3.1. Neuropsychological assessment results analysed by family history categories *340*
9.3.2. Regression analysis of the quantitative measure of genetic liability and neuropsychological assessment scores. *342*
9.3.3. Summary *344*
9.4. HANDEDNESS VARIABLES IN RELATION TO FAMILY HISTORY WITHIN THE HIGH-RISK GROUP ... 349
9.4.1. Qualitative analysis *349*
9.4.2. Family history and laterality quotients *349*
9.5. FAMILY HISTORY FOR SCHIZOPHRENIA ACCORDING TO SYMPTOMATOLOGY AS MEASURED ON THE PSE. 350
9.5.1.Statistical analyses *350*

9.5.2 Results; symptoms and genetic liability *350*
9.6.1 Relationship between social factors and maternal /parental family history within the high-risk group *351*
9.6.2. Comparison of social variables for offspring of affected mothers versus those of unaffected mothers *351*
9.6.3. Comparison of social variables for offspring of affected parents versus those of unaffected parents within the high-risk group. *353*
9.7. DISCUSSION 355

CHAPTER TEN: SUMMARY AND CONCLUSIONS **359**

BIBLIOGRAPHY **365**

BIBLIOGRAPHY OF HIGH RISK STUDIES **409**

APPENDICES **439**

APPENDIX 1 APPENDIX TO CHAPTER 2, SECTION 2.6.14 439
Table 2.6.14.1. School difficulties *439*
Table 2.6.14.2. Social work involvement *439*
Table 2.6.14.3. Psychological difficulties *440*
Table 2.6.14.4 Forensic history *440*
Table 2.6.14.5. Educational qualifications *440*
Table 2.6.14.6. Family history *440*
Table 2.6.14.7. Learning difficulties (reading or writing problems) *441*
Table 2.6.14.8. PSE symptoms *441*
Table 2.6.14.9. Social class of origin *441*
Table 2.6.14.10. Drug usage *442*
APPENDIX 2. APPENDIX TO CHAPTER FOUR 443
Table 4.3. Exploratory data analysis, means (standard deviations), and medians (25th and 75th percentiles of the distribution) *443*
Appendix 2. Matrix 4.1. Correlation matrix of neuropsychological test results for the control group. *446*
Appendix 2. Matrix 4.2. Correlation matrix of neuropsychological test results for the high-risk group. *451*
Appendix 2. Matrix 4.3. Correlation matrix of neuropsychological test results for the first episode patient group *456*
Appendix 2. Matrix 4.4 Evaluation of linear predictors *461*
Appendix 2. Matrix 4.4 Evaluation of the linear predictors *463*
APPENDIX 3. APPENDIX TO CHAPTER SEVEN; HANDEDNESS QUESTIONNAIRE 465
APPENDIX 4. APPENDIX TO CHAPTER NINE 468
9.1 Calculation of quantitative genetic risk(Sham's method) for each of the high risk subjects 468
APPENDIX 5. PAPERS DESCRIBING THE DATA PRESENTED IN THIS THESIS 470

Table of Contents: Tables

Table 1.1 Lifetime expectancy of schizophrenia in the relatives of schizophrenics (from data compiled by Gottesman and Shields, 1982). *25*
Table 1.2. Summary of the First Generation High Risk projects; Design and Methods and Aims *53*
Table 1.3. The diagnostic outcome in the first generation HR studies *69*
Table 2.3.1. Family history of psychosis among the High Risk group *84*
Table 2.3.2. Demographic structure of the High-Risk Group. *84*
Table 2.3.3. Demographic structure of the Control Group *86*
Table 2.3.4. Demographic structure of the First Episode group *87*
Table 2.6.1. Distribution of social class of origin at each assessment *93*

Table 2.6.2 Educational Qualifications of the high-risk, control, and 1st episode group at each assessment 94
Table 2.6.3. Description of educational and employment status in the groups 95
Table 2.6.4.Family history of schizophrenia, Control and High-risk groups 95
Table 2.6.5. Age of subjects Gender, marital status and number of children 96
Single 96
Table 2.6.6. Learning difficulties (reading, writing, and speech problems) 97
Table 2.6.7. Other school problems 98
Table 2.6.8. History of psychological difficulties (information updated at each assessment) 99
Table 2.6.9.Forensic history (information updated at each assessment) 100
Table 2.6.10. Social work involvement and appearance before the children's panel 101
Table 2.6.11. Alcohol consumption 102
Table 2.6.12. Current and past drug usage; cannabis 103
Table 2.6.13.1. Present State Examination ratings at each assessment 105
Table 2.6.13.2. PSE Symptoms ever 105
Table 3.1. Neuropsychological Assessment battery: baseline (3 ½ hours) 109
Table 3.2. Neuropsychological Assessment battery: round two (2¼ hours). 110
Table 3.3. Neuropsychological Assessment battery: round three (1 hour). 111
Table 4.1. Inter-rater assessment of the three tests 141
Table 4.4. Linear predictors for each group for the imputation of scores for factor analysis ... 149
Table 5.1 . Neuropsychological variables compared across groups, initial univariate analysis. 181
Table 5.2 CPT-IP distraction and stimulus conditions; unadjusted marginal means presented. 187
Table 5.3. CPT-IP speed and stimulus conditions; unadjusted marginal means presented 188
Table 5.4 Neuropsychological variables compared across groups with NART estimated IQ as a co-variate. 197
Table 5.5. CPT-IP distraction and stimulus conditions; marginal unadjusted means presented. 201
Table 5.6 CPT-IP speed and stimulus conditions; marginal unadjusted means presented 202
Table 5.7a. Rotated factors: variables with loadings greater than 3, variables appear once (in factor with highest loading). 208
Table 5.7b. Total variance explained by each factor. 208
Table 5. 8. Overall differences across the groups in terms of each factor 210
Table 5. 9. Overall differences across the groups for factors 2 to 6 with NART as a co-variate 210
Table 5.10. Means and standard errors from the comparison across groups of each of the composite scores, without controlling for NART 214
Table 5.11. Adjusted means and standard errors from the comparison across groups of each of the composite scores adjusted for NART 214
Table 5.12. Composite CPT z scores for d'prime, z ln randoms, and z log beta, for shapes, numbers, slow/fast, and distraction/non distraction conditions 217
Table 5.13. Composite CPT z scores for z d 'prime, z random, z log beta, for shapes, numbers, slow/fast, distraction/non distraction conditions; adjusted for NART. 217
Table 5.14. CPT-IP composite scores; numbers and shapes, not adjusted for IQ 218
Table 5.15. CPT-IP composite scores; numbers and shapes, adjusted for IQ 218
Table 6.1. Neuropsychological variables compared across groups, initial univariate analysis. 236
Table 6.2. CPT –IP Adjusted means presented (see Table 6.4 for interactions) 239
Table 6.3 CPT –IP Adjusted means presented (see Table 6.5 for interactions) 240
Table 6.4. Summary of F values from repeated measures ANOVAs for the outcome measures of the CPT-IP (d', ln beta, and ln randoms) for the high-risk and control groups; distraction versus no distraction 241
Table 6.5. Summary of F values from repeated measures ANOVAs for the outcome measures of the CPT-IP (d', ln beta, and ln randoms) for the high-risk and control groups; fast versus slow 241
Table 6.6. Neuropsychological variables compared across groups, initial univariate analysis; rounds 1 to 3 244
Table 7.1. Studies comparing handedness in patients with Schizophrenia and controls 265
Table 7.2. Round one assessment of handedness, first demonstration of tasks; number and percentages presented (percentages are presented in bold). 273

Table 7.3. Round one assessment of handedness, second demonstration of tasks; number and percentages presented (percentages are presented in bold). *274*
Table 7.4 Round one assessment of handedness, third demonstration of tasks; number and percentages presented (percentages are presented in bold). *275*
Table 7.5. Round one assessment of handedness, verbal recall of tasks; number and percentages presented (percentages are presented in bold). *276*
Table 7.6. Laterality quotients: comparisons across groups at time one with Kruskal Wallis tests *282*
Table 7.7. Round one % of stable responses across demonstration tasks (3 presentations of items) as a measure of inconsistent hand preference *283*
Table 7.8. Round one % change from verbal recall to demonstration of tasks as a measure of inconsistent hand preference *283*
Table 7.9. Laterality quotients: Paired assessment of Annett versus Oldfield questionnaire *284*
Table 7.10. Laterality quotients: Oldfield handedness classification compared across groups according to differing cut-off criteria *285*
Table 7.11. Laterality quotients: Annett handedness classification compared across groups according to differing cut-off criteria. *286*
Table 7.12. Handedness categorisation according to the Annett classification system *287*
Table 7.13. Number of items on each scale carried out by the opposite hand compared across groups *288*
Table 7.14. Differences between demonstration and verbal recall of hand preference in the groups presented for each scale and differing cut-offs. *289*
Table 7. 15 % of subjects in each group strongly lateralized *290*
Table 7.16. Round one % change from base line to follow-up on demonstration of tasks as a measure of inconsistent hand preference over time *291*
Table 7. 17 Significant correlations between laterality quotients and socio-demographic variables and family history variables (high-risk subjects in bold and patients in Italics) *292*
Table 7. 18. Significant chi-square values for analysis of the Annett handedness classification and socio-demographic variables *293*
Table 8.1. Neuropsychological variables compared across symptom groups (as measured at first assessment) and adjusted for NART (where appropriate). *307*
Table 8.2. Neuropsychological variables compared across symptom groups (symptoms ever rated) *313*
and adjusted for NART (where appropriate). *313*
Table 8.3. Overall differences across the groups for factors 2 to 6 with NART as a co-variate, symptoms at first assessment *315*
Table 8.4. Overall differences across the groups for factors 2 to 6 with NART as a co-variate, symptoms ever *315*
Table 8.5. Adjusted composite scores analysed according to symptom group; symptoms at first assessment *316*
Table 8.6. Adjusted composite scores analysed according to symptom group; symptoms ever *316*
Table 8.8. CPT –IP Adjusted means presented *322*
Table 8.9. CPT –IP Adjusted means presented *323*
Table 8.10. Comparison of neuropsychological functioning in the 'without symptoms' and 'increase in symptoms' groups between the first and second round of assessments *326*
Table 8.11. Comparison of the CPT-IP between the 'without symptoms' and 'increase in symptoms' groups; first and second assessment. *327*
Table 8.12. Breakdown of the socio-demographic variables by symptoms (ever rated) *329*
Table 9.1. Range of genetic liabilities for specific family history *337*
Table 9.2. Baseline neuropsychological variables analysed by family history for schizophrenia categories *346*
Table 9.3. Neuropsychological variables, follow-up data, analysed by family history for schizophrenia categories *347*
Table 9.4. The results of the regression analyses of genetic liability and baseline neuropsychological assessment scores. *348*
Table 9.5. The results of the regression analyses of genetic liability and the difference between time one and time two assessments. *348*

Table 9.6 Comparison of social variables for offspring of affected mothers versus those of unaffected mothers. 352
Table 9.7 Comparison of social variables for offspring of affected parents versus those of unaffected parents. 354

Table of Figures

Figure 2.3.1. Map of Scotland delineating the Health Board Areas and the estimated population of each 88
Figure 4.1. Examples of Plots for a non-normally distributed variable. 143
Figure 4.2. Examples of plots for a normally distributed variable. 144
Figures 5.1a and 5.1b CPT-IP group by speed interactions for log randoms (numbers and shapes) unadjusted analysis 190
Figures 5.2a and 5.2b CPT-IP group by speed interactions for log randoms (numbers and shapes) adjusted for NART 200
Figure 5.3 Plot of unadjusted composite Z scores 212
Figure 5.4. plot of adjusted composite Z scores 213
Figures 7.1 to 7.18 Laterality quotients displayed by scale and group 280
Figure 8.1. Sex by symptom interaction for Hayling type A errors 312
Figure 9.1. Histogram of genetic liabilities for the high-risk group 337
Figure 9.2. Histogram of genetic liabilities for those with affected second degree relatives 338
Figure 9.3. Histogram of genetic liabilities for those with at least one first degree relative affected 338
Figure 9.4. Histogram of genetic liabilities for those with at least 2 affected first degree relatives 339

Acknowledgements

The nature of the Edinburgh High Risk for Schizophrenia Study necessitated the involvement and collaboration of many people for its success. The original idea for the research was conceived by Professor E.C. Johnstone, who along with her colleagues Dr. D.G. Cunningham Owens, and Professor Jonathon Best, secured MRC funding for the five-year period 1994 to 1999.

Thanks are due to my supervisors, Professor E.C. Johnstone and Professor Ronan O'Carroll, for their invaluable guidance and support throughout. Also thanks to my many colleagues during the study, Ann Hodges, Elizabeth Grant, Suheib Abukmeil, Bobby Clafferty, Jane Morris, Heather Whalley, Richard Cosway, Stephen Lawrie, and Patrick Millar.

Special thanks are due to all of the study participants, and their families, as without their commitment to the research this study would not have been possible. Also thanks to the health professionals; psychiatrists, nurses, social workers, and general practitioners, for their co-operation, help and support throughout.

Finally I would like to acknowlege the invaluable computer support and advice I have been given on a continuous basis throughout the project from Gary Blackie. I am very grateful to the staff of the Applied Statistics Research Group at Napier University, Edinburgh, for the many helpful discussions regarding statistical analyses.

In this thesis I present the work, not only of myself, but of my many colleagues and acknowledge that this study was only possible through a great team effort.

Declaration of authorship

My contribution to the Edinburgh High Risk for Schizophrenia Study and to the data presented in this PhD thesis

My primary role was to administer the neuropsychological assessment battery to the study participants. This was conducted solely by myself for the first 4 years of the study, during the last year Richard Cosway, a psychologist, was employed to conduct the remaining assessments. At this time I was responsible for arranging all of the second and third round of assessments, and continued to do some of the assessments, and I was involved in other aspects of the project, including conducting the maternal interviews and organising the data for analysis. The socio-demographic information presented in chapter two was collected by Ann Hodges, Elizabeth Grant, Bobby Clafferty, Professor Johnstone, Jane Morris, Suheib Abukmeil, and Steve Lawrie. The PSE assessments were conducted by Ann Hodges, Bobby Clafferty, Professor Johnstone, Suheib Abukmeil, Jane Morris, and Steve Lawrie. I also was responsible for compiling and analysing the data that appears in chapter two as a follow on to the work of Ann Hodges (Hodges et al., 1999). In addition I helped with the recruitment of the subjects by reading case notes and visiting families etc., which was principally conducted by Ann Hodges, Elizabeth Grant and later by Bobby Clafferty.

The Neuropsychological Assessment data presented here were principally collected by myself and I conducted all the analyses presented here. This work was necessarily the product of a team effort and I acknowledge that this thesis would not have been possible without the work of all those who are mentioned here.

I declare that this thesis is my own work, and the contribution to this thesis of others is clearly documented here and throughout the thesis where relevant.

Abstract

The causes of schizophrenia remain unknown; the only confirmed risk factor for the disorder is a genetic predisposition. Patients with schizophrenia may show cognitive impairments in childhood and the adult relatives of patients with schizophrenia may also show neuropsychological dysfunction. The extent, to which these variations indicate a vulnerability to schizophrenia or are precursors of the disorder, is unclear. The Edinburgh High Risk Study, where individuals at enhanced genetic risk for schizophrenia were recruited as young adults, provides an opportunity of clarifying these issues. A sample of 162 individuals between the ages of 16 and 25 at high genetic risk for schizophrenia, by virtue of having at least two affected relatives, were administered a detailed neuropsychological assessment battery, in addition to assessments in other domains. Subjects were followed up at intervals of 18 months until the end of the first five years or until the development of psychosis. The results were compared to a normal control group (n=34) and to a group of first episode patients with a diagnosis of schizophrenia (n=37). Findings were compared between the three groups and related to indices of the degree of genetic risk, which were also related to the development of psychotic symptoms and handedness. Widespread significant differences in neuropsychological function between the groups were observed. When the differences in intellectual functioning between the groups were taken into account significant differences in executive function, learning and memory, and block design remained. Significant relationships were established between measures of genetic liability and neuropsychological findings, and shift from dextrality. No relationships between measures of genetic liability and development of psychosis were found. Individuals at enhanced risk for developing schizophrenia for genetic reasons inherit not the disorder itself, but a state of vulnerability manifested by neuropsychological impairment occurring in many more individuals than are predicted to develop the disorder. The state of vulnerability is not sufficient for the development of schizophrenia.

Summary of the organisation of the thesis

The purpose of this thesis was to delineate the neuropsychological functioning of subjects in the Edinburgh High Risk for Schizophrenia Study. The study included those at high-risk for schizophrenia by virtue of their genetic predisposition (defined as a family history of schizophrenia in two or more close relatives) and two control groups, one of well individuals, and one of first episode cases of schizophrenia, all of the participants were within the 16-25 year age band. A battery of neuropsychological assessments was administered at baseline and at 18 months intervals until the end of the first five years of the study.

In order to place the study within the context of the research field, the general literature on schizophrenia (including definition, theories of aetiology and possible genetic mechanisms) was reviewed and is summarised in Chapter 1. More specifically, the literature concerning other high-risk studies was reviewed and the summary, along with an extensive bibliography, is presented in Chapter 1 also. In order to place the neuropsychological results in the context of the study, the overall study design, and methods of recruitment and assessment employed in the project (including clinical and scanning methodologies), and the social and demographic histories of the subjects, are all reported in Chapter 2. The neuropsychological assessment battery is outlined in detail in Chapter 3. A detailed description of the exploratory data analyses is given in Chapter 4. A summary of the literature on the neuropsychological findings in schizophrenia and high-risk studies and the results of the baseline analyses are presented in Chapter 5. The results of the followup assessments are presented in Chapter 6. A literature review and analyses of the data concerning hand, foot and eye preferences is given in Chapter 7. This Chapter includes a methodological comparison of two handedness scales and an evaluation of the effect of changes in the definition of hand preference on the rates of handedness. In Chapter 8 the relationship between psychotic symptoms and neuropsychological performance is outlined. In Chapter 9 the neuropsychological results, presence of symptoms and socio-demographic details, are outlined in relation to family history of schizophrenia, using a categorical and quantitative measure of family history. In Chapter 10 the results are summarised and discussed. The contribution of the

findings to the field of schizophrenia research, the strengths and limitations of the study, and suggestions for further research are also given in Chapter 10.
A bibliography for the entire thesis is presented in addition an extensive bibliography of all high-risk studies is presented separately.

Relevant publications based on data that appears in this thesis

The results of the neuropsychological assessments for the first 100 subjects were published last year and a reprint of the paper is included in the thesis.

Byrne, M., Hodges, A., Grant, E., Cunningham Owens, D.G., Johnstone, E.C. (1999) Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS). Psychological Medicine, 29, 1161-1171.

Data from chapters five, eight, and nine were compiled by E.C. Johnstone into the following publication, which was submitted in Summer 2,000 to the Biological Psychiatry. The paper is not included as it is still at the submission stage.

Byrne, M., Clafferty, B.A., Cosway, R., Grant, E., Hodges, A., Whalley, H.C., Lawrie, S.M., Cunningham Owens, D.G., Johnstone, E.C. Neuropsychology, genetic liabiligy, and the development of psychotic symptoms in those at high risk of schizophrenia. Submitted in 2,000 to Biological Psychiatry.

Other relevant papers:

The data appearing in chapter 6 was written up by Richard Cosway, was printed in Psychological Medicine in September 2,000.

Cosway, R., Byrne, M., Clafferty, R., Hodges, A., Grant, E., Abukmeil, S.S., Lawrie, S.M., Miller, P., Johnstone, E.C. (2,000). Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High-Risk Study. Psychological Medicine, 30, 1111-1121.

The social-demographic data and sample description outlined in chapter two, was written up by E.C. Johnstone and will appear in Schizophrenia Research this year.

Johnstone, E.C., Abukmeil, S.S., Byrne, M., Clafferty, R., Grant, E., Hodges, A., Lawrie, S.M., Owens, D.G.C. (2,000). Edinburgh High-Risk Study- Findings after four years: Demographic, attainment and psychopathological issues. Schizophrenia Research (in press).

CHAPTER ONE: AETIOLOGICAL THEORIES OF SCHIZOPHRENIA AND HIGH-RISK RESEARCH

1.1.Overview of schizophrenia

Schizophrenia, is a low incidence, but debilitating major psychiatric illness, and is estimated to affect approximately 1% of the population. The aetiology of schizophrenia remains unknown, despite more than a century of research into the possible causes. Research into schizophrenia has been multidisciplinary with efforts being made by professionals from many areas including various branches of medicine, not least psychiatry, the basic sciences, and from the social and psychological domains. Methodological difficulties abound in the literature. The most basic and key problem has been the lack of a precise and universally accepted definition of the disorder. There are many theories attempting to account for the occurrence of schizophrenia, they include a variety of genetic, and environmental theories, and various combinations of both. Many hypotheses about the aetiology of schizophrenia have been tested over the years. To date, a myriad of putative risk factors have been postulated, however, the only confirmed risk factor is a genetic predisposition.

1.2 Background and diagnosis

Emil Kraepelin first described 'Dementia praecox' in the 1890's. Bleuler, who believed that schizophrenia was in fact a group of disorders, later coined the term schizophrenia. The European description of schizophrenia remained restrictive while the American concept of schizophrenia expanded under the influences of psychodynamic theory. In the 1970's the need for a universally acceptable definition of the disorder was recognised and spurred by the US-UK diagnostic study (Cooper et al., 1972). In 1973 a task force was set up to develop the Diagnostic and Statistical Manual- third edition (American Psychiatric Association, 1980) with the aim of creating a standard method of diagnosing the disorder agreeable internationally. The DSM-III was later revised and upgraded and the latest edition is DSM-IV (American Psychiatric Association, 1994). A conceptual framework of schizophrenia emerged with the Kraepelinian delineation of the disorder, and the dichotomising of the major psychoses, and it has changed very little since that time. It is within this framework that schizophrenia research has been conducted (Jablensky et al., 1993; Jablensky, 1997).

Schizophrenia is characterised by disturbances in several of the following areas; form and content of thought, perception, affect, sense of self, volition, relationship to the external world and psychomotor behaviour (American Psychiatric Association, 1987). Patients often display thought disorder, which is characterised by loosening of associations, and may be manifest in poverty of speech or incoherent speech. The content of thoughts is disturbed by delusional beliefs, which include those of thought broadcasting, thought insertion, thought withdrawal, and delusions of being controlled. The Patient often experience hallucinations, these are most commonly auditory in nature (voices), however they can occur in any modality. The affect is usually flat or inappropriate, and there is a loss of ego boundaries. The patient experiences a disturbance of self-initiated, goal directed behaviour, which may impair work or other functioning. The persons interpersonal functioning is also impaired. They are often socially withdrawn or emotionally detached. Disturbances of psychomotor behaviour may be present for example catatonic stupor may exist, also stereotypies and bizarre posture may be assumed. The symptoms and signs of schizophrenia are generally described as positive or negative. Positive symptoms include loose associations, hallucinations, bizarre behaviour, delusions and disorganised thinking. In contrast, negative signs include flattening of affect, poverty of speech, social withdrawal, cognitive deficits, attentional deficits, and catatonia (Andreasen and Olsen, 1982).

1.3 Epidemiology

Epidemiological studies of psychiatric disorders began with the work of Jenny Koller in 1895 when she conducted a case-control study of the aggregation of psychiatric disorders in families in Zurich (cited by Jablensky, 1997). Since that time epidemiological methods have been used to study the pattern of schizophrenia in populations and across cultures, and have helped much in describing how and when it occurs, how often, who is most at risk, and patterns of any gender differences. Epidemiological studies have also been used to investigate the role of putative risk factors for schizophrenia.

From epidemiological studies conducted over the century, we know that the lifetime risk for schizophrenia in the general population is approximately 1% (Jablensky et al., 1992), based on a restrictive definition of the disorder. The World Health Organisation's Determinants of Outcome of Severe Mental Disorders investigation (Jablensky et al., 1992) was conducted at 12 centres in 10 countries and was the first transnational research investigation to study contemporaneous and comparative incidence rates for psychiatric disorders among populations. Using a broad diagnosis of schizophrenia incidence rates ranged from 16 to 42 per 100,000, while using a restricted and narrower definition the incidence ranged from 7 per 100,000 in Århus, Denmark to 14 per 100,000 in Nottingham with a mean rate of 10 per 100,000. In all areas there was an excess of males in the 15-24 year age group and females were over-represented in the 35-54 year age group, however, the lifetime morbid risk was the same for males and females. This consistency of incidence across populations despite different cultural, health and climatic differences suggests that these factors may have little effect on the development of the disorder and emphasise a genetic basis. Alternatively, it could suggest that schizophrenia is not an aetiologically homogeneous disorder, and may in fact represent a syndromal admixture (Gibbons et al., 1984).

In the ABC (age, beginning, course) schizophrenia study (Hafner et al., 1998), conducted in Mannheim, a prodromal phase of approximately 5 years was reported in 73% of the cases, also a psychotic prephase (time from first psychotic symptom to climax of first episode) of 1.1 years was noted (Hafner et al., 1995). The investigators, concerned with the reason for the known sex difference in age at onset, found there was a 3-4 year mean age difference between males and females according to any definition of onset. It has been suggested that in women the effect of oestrogen may be protective (outlined by Hafner et al., 1999). Post-mortem animal studies were conducted and the results lend some credence to this theory (Hafner et al., 1991). The question of whether the age at onset differential between males and females is a true biological phenomenon or one mediated through socio-demographic factors, such as marriage, has been studied and there is some evidence for the mediating role of such factors (Jablensky and Cole, 1997).

There have been several reports of a decline in the first admission rates for the diagnosis of schizophrenia after the 1960's (e.g. Eagles and Whalley et al., 1985; Munk-Jorgensen, 1986; Der et al., 1990). Methodological changes in recording may be responsible, such as an increasing reluctance to immediately diagnose schizophrenia, or a restriction in the diagnosis. The reported decline in schizophrenia has been accompanied by an increase in the diagnosis of other disorders (e.g. Munk-Jorgensen, 1986). Hafner and an der Heiden (1997) suggested that the decline seen in the rates of schizophrenia are likely to be methodological artefact rather than a true decrease in the disorder.

In terms of the prevalence of schizophrenia, there are some outlier populations which have been described for many years including the increased prevalence among the Northern Swedish area (Book, 1953) and the west of Ireland and a possible low prevalence rate reported from Papua New Guinea (Torrey et al., 1974). Differences in prevalence rates may be explained in terms of selective migration, as increased incidence rates have not been reported in these groups. There have also been reports of increased incidence rates of schizophrenia among immigrant groups, reported as long as go as 1932 (Odegård, 1932), and particularly among the Afro-Caribbean community in the UK and especially in the second generation (e.g. Harrison et al., 1988; Harrison, 1990), and also among the immigrants from Surinam and the Dutch Antilles in the Netherlands (Selten and Sijben, 1994). The major problem with such studies is that the size and age structure of the immigrant groups remains unprofiled and therefore the accuracy of the findings cannot be confirmed. The possibility that the findings are due to an ill-defined denominator cannot be ruled out (Jablensky, 1995). A study by Hutchinson et al., (1996) reported that there was an increased risk for schizophrenia among the siblings of second-generation Afro-Caribbean probands but not their parents, suggesting an important role for some environmental factor in the aetiology of schizophrenia (reviewed by Eagles, 1991; Harrison, 1990)

1.4. Aetiological theories

1.4.1 Genetics

The only confirmed risk factor for schizophrenia is a genetic predisposition for the disorder. Evidence from twin studies suggests that there is approximately a 50% concordance between monozogotic twins for the disorder (Torrey, 1992). The mode of genetic transmission is not known, however, it is unlikely to be a simple Mendelian mode of inheritance and is most likely to be transmitted by polygenic inheritance (Sham, 1996). The popular liability-threshold model of the disorder suggests that other factors, physical, environmental, hormonal etc. impact on the individual and interact with the genotype and result in the emergence of the disorder.

A genetic predisposition for the illness is not sufficient for the phenotypic expression of the disease. The genetic risks are outlined in Table 1. It is likely that a genetic predisposition in conjunction with agitating and stressful events (physical and/or social) lead to the development of the disease. There are many problems with the genetic theories of schizophrenia: 1. The mode of inheritance is unknown, although various models have been postulated. 2. What exactly is transmitted remains unknown despite the efforts of molecular genetics, and a few promising leads (Moldin and Gottesman, 1997 for review).

Many have argued that although familial this is not synonymous with "genetic" since familial could result from family upbringing practices or circumstances. Studies confirming the importance of genetics include adoption, twin, family, and fostering studies. Twin studies do not allow for reliable differentiation between environmental and hereditary factors as most monozygotic twins share similar environments, and the numbers of MZ twins studied that were reared apart are very small (Gottesman and Shields, 1982). The adoptees family design, involves, selecting as probands, those who are schizophrenic and investigating the rate of illness in the biological relatives. These studies have shown that schizophrenia is more common in the biological families of the adoptees than in the adoptive families. The best known adoption study is the series of studies known as the Danish-American Adoption Study (Kety, 1987, 1988; Kety et al., 1975, 1976, 1994; Rosenthal et al., 1971; Wender et al., 1971). The

importance of genetic factors was confirmed in these studies, however the family environment of the adoptive children was not studied. The Finnish adoption study of Tienari et al is the largest adoption study and is based on a total population of adopted away children of schizophrenic mothers between 1960 and 1979 (Tienari et al., 1985; Tienari, 1992; Tienari and Wynne, 1994). The significance of genetic factors were confirmed in this study but also the role of psychological factors connected with the rearing environmental were implicated, indicating the presence of an interaction between family environment, namely communication deviance in parents, and genetic risk for the development of thought disorder. This fits with one of the models proposed by Kendler and Eaves (1986). Kendler and Eaves, (1986) proposed three models for the joint effect of genotype and environmental liability to psychiatric illness. One of these, genetic control of sensitivity to the environment, provides an explanation for most examples of gene-environment interactions. In this model, genes control the degree to which the individual is sensitive to predisposing risk-increasing aspects of the environment or to the protective, risk-reducing aspects of the environment. Kety (1983) found that even half siblings of schizophrenic probands sharing the same father had higher rates (13%) of illness compared to controls (1%). They argued that as they had different mothers, thus different intrauterine environments and upbringings that those environmental factors are of little importance as confounders.

It is important to comment on the issue of diagnostic diversity in these studies. The Finnish adoption study is the only one that was designed with operational diagnostic criteria at the outset. Most adoption studies predate the use of operational research criteria, which, at least, was not built into the original design. Historical concepts and changes in diagnoses preclude comparisons or at least greatly limit comparability across studies, particularly European and American studies. The stricter DSM-III criteria for schizophrenia spectrum disorders was applied to the original work of Kety et al., (1976) in the Danish Adoption Study (Kendler et al., 1981a, 1981b, 1994; Kendler and Gruenburgh, 1984; Kety and Ingraham, 1992) and proved much more restrictive than the original concept of 'spectrum disorder' and it increased the magnitude of the genetic effect. The refining of the diagnoses over the years has enhanced the reliability in genetic studies, and improved the repeatability of research

findings However, adoption is an abnormal event and such studies may have higher rates of pathology anyway especially antisocial traits. Placement for adoption may not be random and agencies may seek to find a good match with respect to characteristic in biological parents (McGuffin et al., 1994, page 35-36). The adoption studies have been reviewed (Kringlen, 1991; Tienari and Wynne, 1994). Bias in twin and adoption studies has been addressed by Mitchell and Wainwright (1994).

In Table 1 the genetic risks are presented. They were estimated from family, twin and adoption studies, and reported by Gottesman and Shields (1982). From Table 1 it can be seen that schizophrenia is more common in the children of patients than in their parents or siblings, despite the fact that they are all first-degree relatives. Also the offspring of schizophrenic mothers are more often schizophrenic than the offspring of schizophrenic fathers (e.g. Mortensen et al., 1999) suggesting the role of learned psychotic behaviour (Portin, and Alanen, 1997). However this might suggest that the mechanism of genetic anticipation may be involved. The rate of schizophrenia in the offspring of the normal co-twin of a monozygotic discordant pair is the same as that for the offspring of the ill twin and equal to offspring in general (Fischer, 1971; Gottesman and Bertlesen, 1989). This suggests that some factor, perhaps non-genetic, can cause the differential expression of the schizophrenic genotype in the twin pair, given that they are genetically identical.

The mode of inheritance is not known. Most agree that the mode of inheritance is not a simple Mendelian transmission but that it is probably polygenic, and many genes of small effect at different loci contribute to the liability to schizophrenia. Heritability is the proportion of the total variance caused by genetic differences, it is population dependent, and is measured for a particular population at a particular time. It varies between 0-1 (or expressed as %) and is estimated to be some where between 0.6 and 0.7, or 60 and 70% (Bromet and Fennig, 1999).

Table 1.1 Lifetime expectancy of schizophrenia in the relatives of schizophrenics (from data compiled by Gottesman and Shields, 1982).

Relationship	Percentage schizophrenic (%)
Parent	5.6
Sibling	10.1
Sibling (when one parent also affected)	16.7
Children	12.8
Children (both parents affected)	46.3
Uncles/aunts/nephews/nieces	2.8
Grandchildren	3.7
Unrelated	0.86
Monozygotic twins	46.0*
Dizygotic twins	14.0*

* Probandwise concordance in schizophrenia twin studies (weighted average, from Gottesman and Shields, 1976).

McGuffin et al., (1987) concluded in favour of quantitative rather than qualitative differences between the various subtypes of schizophrenia and suggested that they occupy different thresholds on a multiple threshold liability continuum. More severe disorders have higher genetic loadings than less severe ones. It must be remembered that on average 60% of patients with schizophrenia have neither a 1st nor 2nd degree relative with the illness (Bleuler, 1978). It is argued that non-genetic 'phenocopies' (forms of illness clinically indistinguishable from schizophrenia but which are caused by environmental agents or processes) constitute a substantial proportion of schizophrenia and are characterised by a neurodevelopmental disorder (Murray et al., 1985). It must also be remembered that assessing true family history is a very difficult task and in the literature a very broad range of assessment has been used, ranging from finding a reference in the case notes about family history to detailed interviewing of all family members. These methodological differences are likely to lead to different estimates of familiality.

Psychiatric disorders can be thought of as quasi-continuous in the sense that the affected portion of the population can be graded along a mild to severe continuum. It could be postulated that there is an underlying liability to develop the disorder, which is continuously distributed in the population even though it cannot be directly

measured and only those with liability exceeding a certain threshold will manifest the condition. The liability/threshold model holds that a phenotype is due to a mainly additive combination of genetic and environmental effects (Gottesman and Shields, 1982; McGue et al., 1995; Cloninger, 1994).

Models of single genes with incomplete penetrance have been proposed (penetrance is the probability of manifesting a trait given a particular genotype; McGuffin et al, 1994). A single major locus inheritance, modified by variable expression, or incomplete penetrance, can be thought of as liability/ threshold model if the trait is influenced by environmental factors. It provides the theoretical basis for the application of genetic linkage strategies to the study of complex disorders. In its pure form it states that a single gene is the only source of resemblance between relatives i.e. that family environment and 'polygenic' background genetics do not influence the gene. Mixed model seems more plausible (Morton, 1982). Both a major gene and polygenic and/or multifactorial environment may contribute to the familiality of a trait. Polygenes and / or multifactorial environmental effects influence the penetrance of the main gene. Irregular phenotypes like schizophrenia may result from the co-action or interaction of a handful of genes (Risch, 1990).

1.4.1.1 Segregation analysis

The expectations for patterns of disease segregation in families vary according to the mode of inheritance. Possible models of inheritance include sporadic, single gene (dominant, co-dominant, recessive), two genes, polygenic, and multifactorial. Datasets can be tested to provide a statistical evaluation of the ability to conform to particular models, and a model of best fit is selected. The method of family selection is very important in such studies. If the underlying liability is polygenic or multifactorial it can be assumed to have a normal distribution (or one that can be transformed to normal). Relatives of affected members have increased liability compared with the general population so the overall distribution is shifted to the right.

In segregation analysis information is used about entire pedigrees. Segregation analysis has led to many proposed models of transmission. The most commonly applied procedures are based on the mixed model of Morton and McLean (1974) where it was postulated that liability to develop the disorder depends upon the combination of a major-gene effect, a residual environmental component and a multifactorial effect (non-genetic familial effects). It is a combination of the single major locus, and a multifactorial model. It has also been suggested that schizophrenia may be transmitted as an autosomal-dominant gene disorder in some cases (Book et al., 1978).

1.4.1.2. Linkage studies

In genetic linkage studies, the co-segregation of a genetic marker and a disorder is investigated with the aim of detecting departures from independent assortment and of estimating the amount of recombination between the marker and disease (McGuffin et al., 1994). Linkage analysis consists of finding a polymorphic genetic marker that is close enough to the disease on the same chromosome for them to be inherited together with the gene mutation from one generation to the next (McGuffin et al., 1994). The search for linkage in schizophrenia has included the study of HLA genes (Baron, 1986; Kendler, 1986). Chromosomal abnormalities such as fragile sites (Chodirker et al., 1987), and translocations have been reported, as have sex chromosomal abnormalities (reviewed by DiLisi et al., 1994). The findings are inconclusive.

Some specific chromosomes have been implicated (see Moldin and Gottesman, 1997; Gottesman and Moldin, 1997). There are many reasons why segregation analysis may be inexact including diagnostic difficulties, sampling biases, ascertainment biases, and variable age at onset (Kendler, 1986). Another problem with molecular genetics is that one genotype can give rise to clinical diversity, so called pleiotropy, and there is also the problem of genetic heterogeneity (one syndrome, many causes).

Another view is that the gene is one that causes aberrant neurodevelopment, which predisposes the individual to later schizophrenia. "We should not expect to find a gene that codes directly for 1st rank or negative symptoms. Instead we may find a defect

in the control of neurodevelopment which produces some structural change that predisposes to later schizophrenia " (Jones and Murray, 1991, page 620)

There has been a search for biological markers of schizophrenia, markers "higher" than chromosomal aberrations but "lower" than full psychiatric diagnosis (Andreasen et al., 1988). One of the candidates has been smooth pursuit eye movements (SPEM's; Holzman et al., 1973, 1974). HLA genes as markers have also been investigated (Baron, 1986; Kendler, 1986). More specific markers have been investigated in high-risk studies and will be discussed later

1.4.2. Neurodevelopmental theories of the origin of schizophrenia:

1.4.2.1 Overview of neurodevelopmental theories

This section refers to schizophrenia generally. There is evidence to suggest that schizophrenia may be a disorder of neurodevelopment. It has been suggested that the operation of adverse genetic and/or environmental factors, early in foetal life, causing disruption of foetal neural development (Murray and Lewis, 1987; Weinberger, 1987; Lewis, 1989; Lyon et al, 1989; Murray et al, 1991) leads to the development of the symptoms of schizophrenia in adulthood. The evidence for a neurodevelopmental form of schizophrenia comes from clinical studies, neuro-imaging, neuropathology, and from epidemiology. The onset of symptoms in schizophrenia is often preceded by long standing disturbances of cognition, affect and social behaviour (poor premorbid adjustment). Neuro-imaging and neuropathology studies have indicated the presence of brain abnormalities, which are developmental in origin rather than degenerative in nature. Also obstetric complications are reported to be increased in those with schizophrenia (Geddes et al., 1999; Geddes and Lawrie, 1995 for review). Epidemiological evidence includes the findings that patients with schizophrenia are more likely to be winter born (Torrey et al., 1997 for review; Mortensen et. al., 1999). Also maternal exposure to the influenza virus in pregnancy has been shown to increase the risk for schizophrenia in the offspring (Mednick et al., 1988; O'Callaghan, Sham et al., 1991), however a positive association has not always been found (Westegård et al., 1999). Infections during childhood, particularly with Coxsackie B5, have also been found to increase the risk for schizophrenia in adulthood (Rantakallio et al., 1997).

When compared to controls, patients with schizophrenia display increased levels of minor physical anomalies, (Green et al., 1987; Lane et al., 1997), dermatoglyphic abnormalities (Cannon M, et al., 1993) including an increase in fluctuating asymmetry (Mellor, 1992), and ambiguous handedness (Satz and Green, 1999 for review).

1.4.2.2. Precursors of schizophrenia

There is evidence to suggest that individuals who later develop schizophrenia display disturbances of motor development in infancy, Walker et al., (1994) reported limb and movement abnormalities and hypo-tonicity in pre-schizophrenia infants. Patients with schizophrenia were noted to have less positive emotion in facial expressions than controls (Walker et al., 1993). Neurological 'soft' signs (NSS) are abnormal responses to motor or sensory tests in the neurological examination in the absence of other features of a fixed or transient neurological lesion or disorder (Shaffer et al., 1983). By themselves they do not indicate any clearly recognisable central nervous system (CNS) lesion, but rather, are indicative of non-specific brain damage (Kennard, 1960; Mosher et al., 1971). Evidence from several authors suggest that neurological impairments occur more frequently in patients with schizophrenia than in non-psychiatric control groups. Quitkin et al., (1976) reported that neurological soft signs in schizophrenia are correlated with academic and social difficulties, psychomotor deficits and also an earlier age of onset. Neurological soft sign dysfunction is reported to occur in 29-80% of patients with schizophrenia, compared to a prevalence of 5% in non-psychiatric controls (Kolakowska et al., 1985; Woods et al., 1986; Heinrichs & Buchanan, 1988). Lane et al., (1996) reported that 98% of patients in their sample had at least one NSS. The weight of evidence suggests that there is some non-specific brain dysfunction in patients with schizophrenia, present before the onset of the illness, and suggesting a role for early developmental disturbance in schizophrenia. Two cohort studies in Britain (Jones et al., 1994, and Done et al., 1991, 1994) suggested that those who became schizophrenic displayed increased speech difficulties, motor abnormalities and IQ deficiencies in childhood, compared to controls lending credence to neurodevelopmental theories.

1.4.2.3. Neuro-imaging

The findings of brain imaging studies indicate that the brains of patients with schizophrenia have abnormalities of cerebral structure. These include, increased ventricular volume (Johnstone et al., 1976; Lewis, 1990), cortical sulcal widening (Weinberger et al., 1979), sylvian fissure widening (Schwartz et al., 1992), increased cerebral spinal fluid volume (Weinberger et al., 1979; Andreasen, et al., 1990) volume reduction of thalamus (in males) and volume increase in the anterior temporal horn (Andreasen et al., 1990), volume increase in left anterior temporal horn of ventricle (Degreef et al., 1992), temporal horn abnormalities (Johnstone et al., 1989), corpus callosum alterations (Woodruff et al., 1995, for meta-analysis), decrease in cerebral size (Andreasen et al., 1986; Johnstone et al., 1989), volume reduction of temporal lobe (Suddath et al., 1989; Bogerts et al., 1990; Rossi et al., 1990), and volume reduction in hippocampal/ parahippocampal gyrus (DeLisi et al., 1988), however recent work indicates that this may be due to degeneration after illness onset (Razi et al., 1999, for review). There is some evidence from controlled CT and MRI longitudinal studies suggesting that cerebral ventricular enlargement and hemispheric volumetric reductions (e.g. cerebral atrophy) may have a progressive component in patients with schizophrenia (reviewed by DeLisi, 1999). However these may be due to imaging artefacts and continued evaluation is required.

Imaging studies have provided evidence that the types of abnormalities occurring in the schizophrenic brain may not be degenerative in nature but could be developmental in origin, however not all authors are in agreement. Key to the neurodevelopmental hypothesis of schizophrenia, is the theory that the disruption occurs in the foetal environment, therefore it is necessary to establish the extent to which abnormalities are present at or before the time of onset as direct evidence of early disturbance (Waddington, 1993). A number of authors have suggested that the ventricular dilation associated with schizophrenia, the most reproduced abnormal cerebral finding, is not degenerative in nature (Weinberger et al., 1982; Nasrallah et al., 1986; Reveley, 1985) with other researchers opposing this view (Kemali et al., 1989; Woods et al., 1990). The reported lack of correlation between increased ventricular brain ratio (VBR) and

length of illness (Andreasen et al., 1982; Weinberger et al., 1979; Owens et al., 1985) and the finding that an increased ventricular brain ratio is present at and before the age at onset (Weinberger et al., 1982; Waddington et. al. 1991; O'Callaghan et al., 1992) support the hypothesis that schizophrenia is a neurodevelopmental disorder. Studies of ventricular enlargement may be confounded by the fact that ventricular and cortical size increase with age in normal individuals however this effect is not believed to be any greater in patients than controls (Zipursky et al., 1988). The finding of areas of brain abnormality in schizophrenia is consistent across studies however, no specific sites of abnormality have uniformly been implicated in all studies, but ventricular enlargement has been the most consistent finding (Chua and McKenna, 1995, for review). The differences are likely due to methodological problems including, small samples, or inadequate controls, or perhaps to aetiological heterogeneity. The functional imaging literature was also reviewed by Chua and McKenna (1995) and they suggest that schizophrenia is marked by complex alterations in regional patterns of brain activity, not limited to specific areas. This area of investigation is advancing rapidly with increasing technological advances and the implementation of more creative experimental paradigms.

1.4.2.4. Neuropathology

Additionally, the neuropathological studies of schizophrenia point to a prenatal developmental arrest (Murray et al. 1992). Of interest in this regard is the report by Jakob and Beckmann (1986) who described abnormalities in the entorhinal cortex of some schizophrenics which they interpreted as being of neurodevelopmental in origin and which they timed to the fifth month of gestation. More recently, Akbarian and colleagues (1993) described an alteration in the normal distribution of nicotinamide-adenine dinucleotide phosphate diaphorase (NADPH-d) immunoreactive cells in the frontal cortex of schizophrenics. They suggest that this abnormality is likely to originate in the second trimester of foetal development and result from either an alteration in neuronal migration or pre-programmed cell death.

Any disease process causing neuronal degeneration after the third trimester of foetal life will cause a proliferation of glial cells (Waddington, 1993). Neuropathological studies

failed to show gliosis in the brains of some patients with schizophrenia, confirming that these abnormalities are developmental in origin and not the result of a degenerative process (Jakob and Beckmann, 1986; Weinberger, 1987; Bruton et. al., 1990; Benes, 1991). Other neuropathological studies have reported decreased cell numbers (Falkai and Bogerts, 1986; Jeste and Lohr; 1989) and cytoarchitectural abnormalities in certain brain areas that have the characteristics of disturbed cell migration (Jakob and Beckmann, 1986; Arnold et al., 1991) that can only occur prenatally. Studies investigating hippocampal morphology in schizophrenia have demonstrated reduced volume of the hippocampus (Bogerts et al., 1985; Jeste and Lohr, 1989; Suddath et al., 1990), pyramidal neuron loss (Falkai and Bogerts, 1986; Jeste and Lohr, 1989) and decreased pyramidal neuron size (Benes et al., 1991). However increased neuronal density has also been reported (Selemon et al., 1995). Furthermore, absence of increased glial cell density in the medial temporal lobe (Roberts et al. 1986), in the hippocampal formation (Falkai and Bogarts, 1986) and in the entorhinal region (Falkai et al. 1988) supports the hypothesis that a developmental hypoplasia rather than a degenerative process is responsible for the hippocampal abnormalities. Reports of pyramidal cell disarray in schizophrenia (Scheibel and Kovelman, 1981; Kovelman and Scheibel, 1984; Conrad et al. 1991) add further support to the neurodevelopmental hypothesis of schizophrenia. The findings of structural brain imaging studies and neuropathological studies, though not unequivocal, have provided a considerable body of evidence in support of the view that abnormalities found in the brains of patients with schizophrenia are neurodevelopmental in origin. Harrison (1999) published an extensive and comprehensive review of the neuropathology of schizophrenia literature.

1.4.2.5. Obstetric complications

Complications of pregnancy and delivery are considered to represent environmental factors that may disrupt foetal development, and evidence suggests that they may be related to the later development of schizophrenia in the offspring (see Geddes and Lawrie, 1995 for review, and Geddes et al., 1999 for meta-analysis). Obstetric complications (OCs) continue to be extensively studied and related to various clinical characteristics, recently it was suggested that OCs are related to early onset of the disorder (Verdoux et al., 1997). Problems with such research are that sample sizes

have been small in individual studies and there is a general problem with meta-analytic studies such that they may be severely biased by the effect of negative studies remaining unpublished. Three studies based on case register data using large sample sizes support the view that OCs are relevant risk factors for the development of schizophrenia (Hultman et al., 1999; Dalman et al., 1999; Byrne et al., 2000).

Methodological variations abound in this area of schizophrenia research: variation in diagnostic criteria, some studies used maternal recall and in general this means that the mothers are not blind to the diagnosis and may therefore report a biased account, others used hospital birth records as their source of data; sample sizes were often modest and the issue of statistical power was not addressed (Parnas et. al., 1982); control samples have varied greatly between studies, some researchers used patients with other psychiatric diagnoses, others, well siblings or normal controls. Although not all reports agree, it can be seen from this review that there is some evidence for an association between OCs and schizophrenia. McNeil and Kaij (1978) concluded that obstetric complications are risk-increasing factors that should be taken seriously in the aetiology of schizophrenia.

The study of monozygotic twins discordant for schizophrenia is the perfect opportunity to estimate the relative contribution of environmental factors while holding genetic factors constant. Studies of OCs in monozygotic twins have been reviewed by Pollin and Stabenau (1968) and McNeil and Kaij (1978), and studies on this subject include those by Reveley et al. (1984) and Onstad et al., (1992). Reveley reported an excess of OCs in the 5 of 12 twin pairs and in all cases the OCs had occurred in the index case. However Onstad et al., reporting on 16 pairs of monozygotic twins discordant for schizophrenia, found that OCs had occurred in 7 of the pairs but that the well twin was the weakest at birth more often than the ill co-twin. The results of twin studies are similar to those involving singletons; while inconclusive, there are indications that OC's occur in higher frequency in the ill twin of a pair of monozygotic twins discordant for schizophrenia. However twinning by itself is an abnormal obstetrical event.

The exact nature of the OCs, the timing of their occurrence and the factors which mediate the link between them and the later development of schizophrenia have yet to be defined. McNeil and Kaij (1978) suggest that the common consequence of several birth complications may be transient anoxia. Anoxia in the developing brain even for limited periods is known to cause major disruption in brain development, and commonly leads to periventricular haemorrhagic lesions (Larroche, 1984). Recent reports implicate the role of hypoxia in mediating the link between OCs and schizophrenia (Zornberg et al., 2000). OC's tend to be related to increased ventricular brain ratio (Lewis et al., 1989). How the lesion specifically results in the later development of schizophrenia may be a matter of timing, of severity, or it may be just one factor in a multifaceted process of pathogenesis, the true answer remains a mystery. Correlations between OCs, brain abnormalities, and the clinical course and outcome of the disorder have been elaborated upon. Owen et al., (1988) found that patients with a definite OC presented at an earlier age and also larger VBRs when accompanied by widening of cortical sulci and fissures occurred more commonly in subjects with OC's than in those without (Owen et. al., 1988). In the Copenhagen high-risk study (Mednick et al., 1987), larger ventricles were associated with more difficult pregnancies and deliveries, also low birth weight was found to be an especially strong predictor of ventricular brain ratio. Obstetric complications were found to be related to increased ventricle size, and tended to be more common in non-familial patients with schizophrenia (Lewis and Murray, 1987). However there is some evidence for an interaction between genetic predisposition and OCs (Cannon T, et al., 1993).

An interesting theory was put forward by Goodman (1988) where he suggested that foetuses who are already abnormal or vulnerable in some manner are more likely to experience OC's and that rather than being a cause of schizophrenia, OC's and schizophrenia are effects of some other underlying and as yet, unspecified, pathological process.

1.4.2.6. Season of birth

One well replicated finding in schizophrenia research is the over-representation of individuals born in the late winter or early spring months. In a recent review (Torrey et

al., 1997) of some 250 published studies, a remarkable consistency was reported in the finding of winter/spring birth excess. An estimated 5-8% excess was reported. Statistical artefacts could not account for the findings. Such artefacts as the age incidence and age prevalence effect suggested by Marc Lewis (1989)- that is, persons born in January are older than those born later in the year within the same age category and therefore have spent more time at risk for schizophrenia. The significance of this finding in terms of the aetiology of schizophrenia remains unclear. However it could be that birth in the early months of the year is associated with an increased risk of cerebral damage, caused by some seasonally varying environmental factor, which predisposes to later schizophrenia. If this seasonally varying environmental factor is causally related to the later development of schizophrenia, patients with no obvious genetic predisposition should more often be winter born than those at high genetic risk and there is evidence to support this theory (Kinney and Jacobson, 1978; McNeil, 1988; Shur, 82; O'Callaghan, Gibson, et al., 1991). However the confinement of this effect to those without increased genetic risk was not replicated in a large Danish cohort (Mortensen et al, 1999) and it could be that the seasonally varying factor interacts with genetic predisposition in a non-additive manner. A strong effect of urbanicity in increasing the risk for schizophrenia has been reported (e.g. Mortensen et al., 1999). This has led to the speculation that the close confines of an urban environment facilitate the spread of an unknown viral infection to pregnant women to increase the risk of later schizophrenia in their offspring.

1.4.2.7. Viral infection hypothesis

The viral infection hypothesis of schizophrenia suggests that the neurological brain abnormalities associated with schizophrenia may be a result of a neuro-active virus causing damage to the developing brain (Waddington, 1993). Epidemiological studies have reported an association between prenatal exposure to the 1957 influenza epidemic and an increased risk of later schizophrenia in Helsinki (Mednick et al. 1988), England and Wales (O'Callaghan, Sham, et al. 1991), Japan (Kunugi et al. 1992), Australia (McGrath et al. 1994), Scotland, and England and Denmark (Adams et al, 1993). Not all such studies have found this relationship (Crow and Done, 1992; Torrey et al. 1988; Westergård et al., 1999). Longitudinal studies over many years also indicate that there

is a consistent relationship between prenatal exposure to influenza and later schizophrenia (Barr et al. 1990; Sham et al. 1992; Takei et al. 1993; Morris et al., 1993). There is little evidence for an association between infectious diseases, in the prenatal environment, other than influenza and influenza related viruses (bronchial pneumonia) and schizophrenia (O'Callaghan et al., 1994). However infections in childhood may be important (Rantakallio et al., 1997).

A temporal window of vulnerability may be present in the developing human foetus to maternal exposure to the influenza virus (Adams et al., 1993). Studies have demonstrated that the association exists following exposure in the second trimester (Mednick et al, 1988; Takei et al., 1996), sixth and seventh month (Barr et al., 1990; Sham et al., 1992; Adams et al., 1993; Takei et al., 1995), fifth month (O'Callaghan, Sham, et al., 1991), and fourth month (Adams et al., 1993), with the effect most prominent among females (Kendell and Kemp, 1989; O'Callaghan, Sham, et al., 1991; Morris et al., 1993; Takei et al., 1993, 1994; Adams et al., 1993). Thus, while the majority of studies indicate a specific vulnerability during some time in the second trimester, the findings have not been entirely consistent and have not pinpointed a precise, crucial period of development. Coffey and Jessop (1959) found more congenital abnormalities of the central nervous system in the female than in the male offspring of mothers who had influenza during pregnancy. The lack of consistency in the findings may relate in part to the difficulties involved in estimating the timing of the exposure.

The major difficulty with drawing inferences from these studies is that they are purely epidemiological and associative in nature and there is no way of knowing whether or not the mothers actually contracted flu as serological evidence is not available. Three studies reported no increase in the risk for schizophrenia in the offspring of mothers who were known to have had influenza (Crow and Done, 1992; Mednick et. al., 1994; Cannon et al., 1996). However the methodology poses some difficulties, with the possibility of serious under-reporting of mothers affected (O'Callaghan, Sham, et al., 1991).

The viral infection hypothesis and seasonality of births in schizophrenia fit together well. Viral infections are more widespread in the winter months and could contribute to the seasonality of birth effect in schizophrenia. This weight of evidence suggests a role for viral infection, and particularly maternal influenza infection during the second trimester of foetal life, in the pathogenesis of schizophrenia, however the effect is thought to be a modest one (Sham et. al., 1992). It remains unclear, whether this suggests a purely environmental cause or one genetically mediated, whichever the case, these studies lend credence to the neurodevelopmental hypothesis of schizophrenia.

1.4.2.8. Minor physical anomalies

Minor physical anomalies (MPAs) are benign congenital abnormalities (unusual morphologic features), detectable by surface examination, that are of no serious medical or cosmetic consequence (Smith, 1988). These trivial abnormalities of ectodermal origin are reported to be associated with disruptions of foetal development, usually occurring in the first and second trimester of life. MPAs are most common in areas of complex and variable features such as the face, ear, feet and hands and including such features as widely spaced eyes, epicanthal skin folds, low set ears, abnormally shaped ears and high palates.

The value of their recognition is that they are indicators of altered development. Ectodermal development closely parallels development of the nervous system and so MPAs could provide clues to otherwise hidden foetal neural development. Although little is known about the fundamental processes that control morphogenesis, genetic influences are known to guide the programme (Smith, 1988), but disruption may also be due to environmental factors such as infection, toxaemia, mechanical, vascular, or toxic. Thus MPAs may have a genetic and/or environmental aetiology.

The relationship between MPAs and schizophrenia has been examined. Many studies have confirmed an increased incidence of MPAs in adult schizophrenia, (Gualtieri et al., 1982; Guy et al., 1983; Lal and Sharma, 1987; Green et al., 1987, 1989a; O'Callaghan, Larkin, et al., 1991; Lane et al., 1997; Green et al., 1994; Akabaliev and Sivkov, 1998). However they do not all agree upon the specific clinical correlates of

MPAs. Cognitive impairments and minor physical anomalies were found to be related in a study by O'Callaghan, Larkin, et al., (1991) but not by Guy et al. (1983). An association between early age of onset for schizophrenia and MPAs has been reported in one study (Green et al., 1987, 1989a) but not found in others (Guy et al., 1983; O'Callaghan, Larkin, et al., 1991). Guy et al., (1983) found MPAs to be associated with poor premorbid adjustment while O'Callaghan, Larkin, et al., (1991) found MPAs to be associated with having more obstetric complications, male gender and a positive family history for psychosis. Of particular interest is the finding that MPAs tend to be more lateralized in patients with schizophrenia than in controls (Lane et al., 1997), emphasising the importance of asymmetrical distribution of dysmorphogenic features in schizophrenia. Minor Physical anomalies have also been reported in excess in childhood schizophrenia, (Goldfarb, 1967; Steg and Rapoport, 1975) and in childhood autism (Campbell et al., 1978).

MPAs are of particular importance in relation to the study of dermatoglyphics, as dysmorphogenesis of the hand is known to be associated with altered dermatoglyphics, an extreme example being the unusual palmar creases associated with syndactyly of the phalanges. Bracha et al., (1991) reported that in monozygotic twins discordant for schizophrenia the ill twin demonstrated higher scores on a hand maldevelopment scale than the well co-twin. The scale used, incorporated both MPA and dermatoglyphic variables. Another interesting aspect of this suggested association is the concurrent development of the hand and dermatoglyphic configurations. To date there is no available literature addressing the wider issue of an association between MPAs and dermatoglyphic configurations.

1.4.2.9. Dermatoglyphics

Dermatoglyphics is the study of the ridged skin patterns of the hands and feet. Dermatoglyphic configurations develop in utero and once laid down, they remain absolutely consistent throughout life. Therefore changes in pattern development, in the frequency of rare patterns and/or pattern combinations or in the arrangement of the dermatoglyphics, must be attributed to processes that are prenatally determined. The usefulness of dermatoglyphic analysis in medicine has long been recognised.

Dermatoglyphic abnormalities have been found to be associated with schizophrenia (Bracha et al., 1991, 1992). Dermatoglyphic abnormalities may be useful indices of prenatal developmental insult. Both dermatoglyphics and MPAs represent fossilised evidence of prenatal disturbance.

1.4.2.10 Handedness

Abnormal/ anomalous lateralization has been reported to be associated with many neurological conditions. Lateral preferences may be useful indicators of brain alterations. Studies of lateral preference, and in particular studies of hand preference have been carried out in schizophrenia. A number of investigators have reported finding that patients with schizophrenia have a higher incidence of either non-right handedness or of left-handedness than do normal control subjects (for review see Satz and Green, 1999).

1.4.3. Research on neurotransmission

Biochemical research in schizophrenia has centred on the dopamine hypothesis. According to the dopamine hypothesis of schizophrenia the clinical features of this condition are the result of central dopaminergic hyperactivity. The dopamine hypothesis is primarily based on two central issues. Firstly, neuroleptic medications are effective in the treatment of schizophrenia by antagonising dopamine at synaptic sites (Carlsson and Lindquist, 1963) and secondly, amphetamine and other psychostimulant drugs can induce or exacerbate psychosis. These effects led researchers to believe that schizophrenia could be caused by an excess of dopamine, or that schizophrenics might have too many receptors sensitive to dopamine (Iversen, 1979). It is now known that there are many types of dopamine receptors in the brain with differing functions, and interactions between different neurotransmitters is likely to be also important. A recent review of the issue was conducted by Willner (1997), who outlined the difficulties inherent in the dopamine hypothesis and commented that "the dopamine hyphothesis of schizophrenia has both guided and constrained research; it has been refined, expanded and challenged, but continues to reign supreme. It appears increasingly that this reflects less its intrinsic merits and more the absence of a convincing, comprehensive alternative approach" (Willner, 1997, page 298). The issue is complicated by the fact that

schizophrenia is likely a heterogeneous disorder, and may be expressed through differing symptom profiles in different patients. In conclusion, research on neurotransmission in schizophrenia continues to investigate the role of dopaminergic systems and those of other brain chemicals in response to neuroleptic treatments (Carlsson, 1987; Vollenweider, 1998).

1.4.4. Sociological explanations

The finding of an inverse relationship between schizophrenia and social class is well replicated. The relationship has been well established but its aetiological significance remains unclear. Even with vast changes in diagnosis and systems of describing social class, the finding has remained (Dohrenwend and Dohrenwend, 1969; Eaton, 1980). There are two major theories to account for this relationship. The first, 'the social causation hypothesis' holds that rates of schizophrenia in the lowest socio-economic strata could be disproportionately high because the conditions of life in these strata are somehow conducive to the development of the disorder (Kohn, 1968; 73; 76; Dohrenwend and Dohrenwend, 1969). The second hypothesis known as the social selection /or drift hypothesis (Dunham, 1965), suggests that schizophrenia will occur in all classes in equal proportion. However, the bulk of cases will be found in the lower social classes because it acts as a receptacle for the unsuccessful from the higher social classes. The illness impairs the social class attainment of the individuals and causes a downward drift in social status after onset of the illness. The drift theory has gained the most support. Hafner et al., (1999) found that age at onset for schizophrenia was important for social attainment. Social stagnation (failing to achieve ones social potential) was found to occur in those whose onset was early, with a failure to improve social status like their peers, and those with later onset experience social decline (unable to maintain the social position achieved). Support against the social causation hypothesis is the evidence that the fathers of schizophrenics have the same social class distribution as the general population (Goldberg and Morrison, 1963). In a Dutch cohort (Wiersma et al., 1983) and in the two British cohort studies (Jones et al., 1994; Done et al., 1994), and in an Irish sample (Mulvaney et al., submitted 2000) the fathers of patients with schizophrenia were found to be of a higher social class than the general population.

Life stresses might be possible precipitants of schizophrenia. Stresses such as economic difficulty and physical illness, interpersonal problems with family members as well as neighbours and friends (Neale and Oltmanns, 1980), have been suggested. Two longitudinal studies using repeated measures have provided evidence for a relationship between changes over time in life events stressors and relapse of symptoms (Ventura et al., 1989; Malla et al., 1990).

1.4.5. Family environment

Family dysfunction has been suggested as an explanation for the development of schizophrenia, with the view that the patient is a symptom of a family pathology (Laing and Esterson, 1967). Alanen (1958) found that mothers of schizophrenic children tended not to understand their children's needs and feelings, were over-possessive and often hostile to their children. Mishler and Waxler (1965) claimed that the parents of patients with schizophrenia could be differentiated from parents of other individuals in terms of over-protectiveness, rejection, aloofness, thought disorder, and abnormalities of speech. Bateson et al., (1956) claimed that a particular type of pathological binding, so called 'double-bind', is seen in parent-child relationships of patients with schizophrenia. The double bind consists of a paradoxical communication passed from one person to another; the person is given 'mixed' messages. Bateson et al., (1956) suggests that the potential schizophrenic learns to cope by either withdrawing into his/her own world or by becoming irrational. According to Lidz et al., (1965), the whole family is seen as pathological and the 'schizophrenic ' individual is selected to play scapegoat.

Family environment and stresses in family relationships have also been considered from an aetiological perspective in the social causation issue. Family environment has been considered an important predictor of and probable influence on relapse in schizophrenia (Brown et al., 1972). The concept of expressed emotion has been particularly important in this work. Expressed emotion (EE) is a set of attitudes, types of behaviour and feelings shown by a key relative towards a patient living with him/her. EE is assessed by a standardized interview and the two essential elements of the construct are criticism,

including hostility, and emotional over-involvement by the relative towards the patient. High EE critical attitudes have been reported to predict onset of schizophrenia spectrum disorders in non-psychotic adolescents during a five-year follow-up (Norton, 1982 unpublished doctoral thesis quoted by Valone et al., 1983). Communication Deviance (CD) is another factor related to family environment that has implications for the onset and course of schizophrenic disorders (Miklowitz et al., 1986). Communication deviance is defined as a measure of the degree to which an individual is unable to maintain a shared focus of attention with a listener during verbal transactions (Wynne et al., 1976).

It is unlikely that family dysfunction is at the core of the aetiology of schizophrenia, however studies of EE in families of patients with schizophrenia demonstrate that family functioning does have an impact on relapse rates in the disorder (Brown, et al., 1972).

1.4.6. Conclusion

The theories regarding the aetiology of schizophrenia are multiple and diverse. It is currently believed that schizophrenia is a disorder of the brain. The neurodevelopmental hypothesis of schizophrenia (Weinberger, 1987), suggests that disrupted foetal brain development, leads to the later development of schizophrenia in adult life. This disruption of development could be of genetic and/or environmental origin. It is unlikely that a gene directly coded for the symptoms of schizophrenia will be identified. Jones and Murray (1991) suggested that it is more likely that a defect in the control of neurodevelopment produces some structural brain change that later predisposes to schizophrenia, will be found. The interaction of this biological susceptibility and environmental factors may lead to schizophrenia.

It is therefore important to study the development of those who are 'at risk' for schizophrenia (Table 1), who may carry the putative genes, in an attempt to disentangle the relevant physical, social, and historical events that may be implicated in the development of the disorder in this group.

1.6. High-risk studies of schizophrenia

1.6.1.High-risk (HR) studies

To search for the cause of a disorder is a necessary part of our efforts to try to understand the disorder, with a view to reducing the severity, developing adequate treatments or eliminating the disorder completely. Our understanding of schizophrenia remains limited. Much of the research is conducted on persons who have already manifest symptoms of the disorder leading to difficulties in disentangling the causes from the consequences of the illness.

An obvious and very powerful strategy to identify precursors and follow the dawning and unfolding of an illness is to recruit subjects early in life, and follow them in a systematic and prospective fashion until the onset of illness. To prospectively study the development of a low incidence disorder such as schizophrenia in the general population, with only a 1% morbid risk for the disorder, vast numbers of individuals would need to be studied over long periods of time. This type of research would be hugely expensive and very difficult to implement and follow-up. Large cohort studies have been implemented around the world, for example two British cohorts (1946 and 1958) and a Finnish birth cohort (1966). The incidence of schizophrenia has been identified in these groups and precursors sought from educational, obstetric, and social records from childhood. This strategy falls down, in that the information collected about the child was not done so with the aim of identifying precursors of schizophrenia and so the records were often very general and the approach, retrospective. This criticism is often made of case register based research. In the cohort studies, the number of individuals who become psychotic is likely to be small (Jones et al., 1994, Done et al., 1994) and so statistical power remains limited.

A more powerful method is one where subjects with a known increased risk for a disorder are recruited into a study, designed specifically with the aim of identifying precursors of the disorder, and to examine the development of the illness. It is known that relatives of patients with schizophrenia have a higher incidence of the disorder than those with no family history of schizophrenia so that it makes obvious, scientific and

economic sense to study such a high-risk group. High-risk can have many definitions but here it refers to genetic risk unless otherwise specified. " A high-risk study is a psychological, sociological, and biological investigation in families where there is an illness that seems to be familial and is possibly transmitted on a genetic basis" (Dunner, 1987, page 363). The high-risk strategy is prospective in nature and free from many of the biases of retrospectively collected material. Data is collected prospectively and with the specific purpose of the research in mind, so it can be collected systematically.

1.6.2. The high-risk paradigm; problems, limitations, and necessary considerations.

The high-risk strategy is not without theoretical problems and limitations.
1). The inclusion of offspring of patients with schizophrenia, which has been the design of the majority of HR studies, represents a highly specialised group. Only 10-15% of those who develop schizophrenia have a parent with the disorder, so it may focus on a kind of illness that is different to that in the majority of patients with schizophrenia. This group may represent a subgroup of all patients with schizophrenia who have an atypically strong genetic and environmental diathesis (Hanson et al., 1977). Another assumption is that the genotype transmitted in families is the same type that other (non-familial) persons with schizophrenics get.

2). Because the onset of schizophrenia occurs in early adulthood, often there is a large time gap between recruitment into the study, generally in infancy, and the period of maximum risk. This problem of time between recruitment and period of maximum risk is intimately related to the issue of attrition, which may be great over the course of 20 years or more. The question of when should a study of subjects at risk for schizophrenia begin is a difficult one. Hanson et al. (1977) cautioned " anytime a high-risk child is identifiable on behavioural measures as a candidate for adult schizophrenia, there is a reason to suspect that an important threshold in the disease process has already been passed" (page 584).

3). Sampling bias may occur in the selection of HR subjects. Lewine et al, (1984) found that of 25 genetic risk projects 56% studied only the children of schizophrenic

women, the remaining 11 studies included a mixture of both index mothers (n=606) and index fathers (n=355). However it is believed that there is a roughly equal prevalence rate of schizophrenia in adult males and females (Jablensky et al., 1992). Schizophrenic women are more likely to have children than schizophrenic men, perhaps due to the typically later onset of the illness in females, so there may be more familial schizophrenics with a schizophrenic mother than a schizophrenic father. There is some evidence that the morbid risk is somewhat lower for the offspring of schizophrenic fathers than for the offspring of schizophrenic mother (Mortensen et al., 1999). This may introduce a bias with respect to prevalence rates but also for what may be a systematic sex difference in schizophrenic characteristics e.g. male earlier onset, poor premorbid history and negative symptoms. However there is no evidence that male offspring of female schizophrenics have a more typically female illness profile. The mothers may have a more schizoaffective type illness, and the contribution of the misdiagnosis remains unknown, the earlier studies suffered greatly form lack of diagnostic specificity. The males who do have children may represent a more competent group and less severely ill group than those who don't have children (Lane et. al., 1995).

4). In the early studies there were few operationally defined diagnostic criteria available for selection of samples so the earlier studies suffered from diagnostic uncertainty and lack of specificity for diagnosis. Many samples were later re-diagnosed post 1973, when DSM III was introduced, and subsequently refined. There are issues involved in accurately diagnosing the index cases. Blindness is very difficult to achieve in such studies.

5). The issue of the inadequacy of linear models to explain developmental processes is very important to risk research, where the predictor of future is past behaviour (Meehls Law). This law does not take into consideration future developmental perturbations that may dramatically alter the course of development (Meehl, 1957). Hanson et al. (1990) outlined this idea clearly in the statement " we see predicting future schizophrenia more like trying to predict which high school student will contract encephalitis, sustain brain damage and thus be unable to go to college"

(page 482). They use the analogy that you cannot predict a tadpole turning into a frog on the basis of growth rate, metabolic rate, diet or other physiological property, these are not linear events; some form of biological switch is turned on. "Possibly schizophrenia may represent the turning on or off of developmental switches that send the normal course of development into an entirely abnormal direction" (pg 429). It is easier to look back on the events and make sense of their occurrence, than to predict the outcome from only the premise. This notion was outlined by Freud " The chain of causation can always be recognised with certainty if we follow the line of analysis, whereas to predict it along the line of synthesis is impossible" Freud, (1920, 1955, p168).

6). Over the course of a longitudinal study, the instruments used and the theories driving them may become obsolete. Also measures appropriate at ages 5 or 10 may not be appropriate at later ages introducing a problem of continuity of measures over time.

7). There is a problem with identifying confounding variables in HR research and deciding how best to handle them in analyses. For many studies it has been acknowledged that "intelligence and social class have proven to be pervasive and troublesome sources of confusion in interpreting research results.....should they be controlled as sources of contamination in analysing statistical results or should they be considered as important precursors of schizophrenic disorders worthy of study in their own right?" (Watt, 1984, page 577)

8). Problems exist in comparing studies. For example, some studies included the offspring of dual mated patients (Danish High Risk Study) and this may lead to different results than when the offspring of a single ill parent are included. There will be a heavier psychopathology loading when both parents are affected

9). Typically risk investigators select one child in a family. The decision about who to include may be constrained by the need to fulfil matching criteria, such as age, or gender. The virtue of the single child choice is that it restricts the introduction of

highly correlated data and reduces the weighting provided by larger families. It also eliminates a critical measure of the stability or instability of the family as indexed by the adaptation and competence of all siblings.

10). There is a problem of having highly heterogeneous groups, from many backgrounds gender, age etc. However narrow selection procedures reduce sample variance but are not generalisable.

1.6.3. Goals for HR research

Hanson et al (1977) outlined what they see as three important realistic goals for high-risk research.

The first one is to define the range and specificity of the childhood characteristics that precede adult schizophrenia. Childhood symptomatology is often associated with adult psychopathology, but childhood symptomatology is a poor predictor of adult diagnosis (Fish, 1975; Mellsop; 1973). This is an issue of specificity.

The second goal of high-risk research is to quantify the relation between predictors and outcomes. The usefulness of predictors will be determined by their accuracy, which will be determined only by the eventual outcome in the sample, which may take a very long time. False positive and false negative rates will have to be determined. The issue of sensitivity and specificity of risk indicators in HR populations is of concern to all HR researchers.

The third goal of high-risk research is to determine whether valid childhood predictors of adult schizophrenia identify the etiological roots of schizophrenia. The predictor variables might be indicators of the high-risk genotype, which are associated with the development of schizophrenia and exist in those who have the potential for developing the illness but may remain well. Valid childhood predictors of adult schizophrenia might identify potentiators (Meehl, 1973) or correlates of potentiators that lead to breakdown. An example might be poor scholastic achievement. This may be related to family pathology and the family pathology might be the potentiator of schizophrenia in the predisposed subjects. So while scholastic achievement may be related to the development of schizophrenia it may be

neither a consequence of the high-risk genotype or an early sign of schizophrenic behaviour. Finally childhood predictors may represent an illness that has already begun, these behaviours indicate when schizophrenic behaviours begin but would not necessarily shed light on either the genetic or environmental contributors to the development of schizophrenia. Longitudinal designs don't establish causal relationships but they do offer a unique vantage point for viewing development and making inferences about causal relationships (Watt, 1984). In order to determine the power of the HR method for a particular study, it is necessary to make some assumptions about the mode of inheritance of the biological trait and about its relationship to illness susceptibility. In the sample sizes of HR subjects obtainable in HR studies it may only be realistic to detect genetic susceptibility traits that have a large effect. The difference also between the correlates of illness and predictors of illness must be considered. Early abnormalities do not establish causal relationships and lots of subjects remain well up to the time of the development of the illness. Early behavioural abnormalities often represent the effects of living with a disturbed parent (Lewine, 1984; Bleuler, 1978; Ricks and Berry, 1970) and may represent non-specific environmental effects that would occur to virtually anyone living in a chaotic environment. If such children had been reared in a less chaotic environment they may still have become schizophrenic but the pre-morbid picture would have been very different.

The major issue of HR research is not the differences between controls and HR groups but the search for specific individuals within the HR sample who are most likely to develop schizophrenia in adulthood. Only 10-15% may go on to develop schizophrenia and they may not be so deviant as to pull the mean for the sample a significant distance away from the mean for the control group. McNeil and Kaij (1979) urge caution in the aetiological interpretations of the results of HR studies.

Hanson et al. (1990), reported on an earlier identified group of 5 super high-risk children (Hanson et al., 1976) on the basis of poor motor performance, large intra-individual variances on a multitude of psychological tests, and behavioural problems, and all had a schizophrenic parent, giving an expected rate of 17%, close to the

genetic predictions. However in their early 20s all were doing well and had no psychiatric illness. The rarer a condition the harder it will be to detect. So with an expected base rate of 10% and with specificity of 95% and sensitivity of 90%, the probability of accurately detecting it is only 2/3. This might make intervention appear very successful, as those identified as at risk and treated may never have become ill in the first place (Hanson et al., 1990).

1.6.4. Issue of biological heterogeneity

Who are the invulnerables in the HR sample? Garver, (1987) discusses the importance of trying to identify these "invulnerable" subjects, those without the genotype and those with the genotype but with a buffering mechanism to keep it in check. "To parcel out the effects of psychosocial variables, high-risk populations need to be separated into offspring who are and who are not biologically/genetically vulnerable, since psychosocial modifiers will be interactive only in the biologically vulnerable offspring" (Garver, 1987, page 525), this introduces the problem of biological heterogeneity. "If a non-psychotic sibling is not genetically/biologically predisposed to develop psychosis the pursuit of other protective factors that have prevented the development of psychosis will lead us astray, since the sibling is not at risk" (Garver, 1987, page 526). If several different psychotic disorders make up a heterogeneous group of schizophrenias, each may behave differently in the context of other risk factors that are being observed and quantified in the present HR studies. Some HR study families may include psychotic subjects who do not have a genetic illness but who have been made vulnerable to psychosis for other reasons, e.g. some developmental insult. Such a psychotic illness may behave differently under the conditions of the other risk factors being studied in the HR populations. The additivity or multiplicity of gene-environment interaction may vary for different individuals within the group, making it difficult to identify common and generalisable aetiology factors.

1.6.5. Ethical issues

There are ethical issues involved in High Risk studies. These have been clearly addressed in the literature (Watt et al., 1984). A major concern is how to protect

subjects from unethical exposure or stigmatisation either in his or her own mind or the minds of others regarding a possible eventuality that probably will never occur (Watt, 1984). Professor William Curran of Harvard University acted as consultant on the issue of ethical considerations in risk research, his comments were reported by Garmezy and Phipps-Yonas (1984). He commented that in some ways risk researchers are fortunate, as they are not involved in decisions about withholding drugs, or transplanting organs. However they are greatly involved in issues of informed consent, privacy and confidentiality and the problem of identifying and labelling a child who is at risk. Most risk investigations tap 3 sensitive areas:

1. They are essentially psychiatric studies
2. They examine children, a group most protected by society
3. They usually are long-term prospective studies, which involve unusual obligations over extended periods of time for families who participate. Does informed consent imply a full disclosure of the concepts and consequences of the risk? Does revealing the full nature of the concept cause the parents to alter the environment and it becomes a self-fulfilling prophecy. There are many ethical issues pertaining to HR research.

In summary, high-risk research is fraught with many topical issues among them are those of study design; appropriate samples, adequate assessment strategies, good diagnostic criteria, minimal attrition rates, and careful consideration of ethical issues. All need to be considered carefully in the implementation and continuation of such research.

1.7. The first generation high-risk studies

Many High Risk studies have been conducted with the aim of prospectively identifying subjects who will develop schizophrenia from those who will not within a group of persons at a high statistical risk of developing schizophrenia due to their family history and also to distinguish antecedents of the disorder from secondary deficits associated with the disorder (Asarnow, 1988). There have been many high-risk studies. Fish began the New York infant development study in 1952, which was a small and intensive investigation into the early development of 12 offspring of schizophrenic mothers. The Danish High Risk project was the first large HR study,

beginning in 1962, and comprising 207 offspring of schizophrenic mothers. While many HR studies have been conducted a great diversity exists between them in terms of the composition of samples studied, the age at entry of the subjects, gender, socio-demographic characteristics, parental diagnoses, length of follow-up and assessment emphasis employed. The type of assessments used were closely linked to the theoretical underpinnings of the studies, for example the Danish HR study had as its main focus the hypothesis that subjects at risk for the later development of schizophrenia would display deviant electrodermal activity indicating deviant stress response in these subjects (see Table 1.2). The New York High Risk Study (NYHRS) emphasised impaired sustained attention as a possible marker for genetic risk. These different underlying theoretical perspectives focused the studies in different directions, leading to varied test assessments and great diversity in the results. These differences have limited the comparability of the studies, which have been conducted across continents using different assessments, differing diagnostic criteria, sampling methods, and control groups. No one study is an exact replica of any other and because of this they must be evaluated, each on its own merit, and the combined results must be interpreted with caution. The HR studies have been outlined and the in Table 1.2. The principal investigators, the title of the project, the at risk sample, diagnostic criteria used, the control sample and the sociodemographic characteristics of the groups are summarised, in the Table. This Table was constructed from a collection of sources and original materials including review papers (Garmezy, 1974b; Asarnow, 1988; Erlenmeyer-Kimling and Cornblatt, 1987; Cornblatt and Obuchowski, 1997; Erlenmeyer-Kimling and Cornblatt, 1984), books (e.g. Watt et al., 1984; Rolf and Masten, 1990), special journal issues devoted to updates of the high-risk studies (Schizophrenia Bulletin (1984), 10 (2), Schizophrenia Bulletin (1987), 13 (3); Schizophrenia Bulletin, 1995, 21 (2), 179-239) and also from individual journal articles (Hanson et al., 1977; Itil et al., 1974) and online databases including BIDS EMBASE, PubMed, and PsycInfo. In 1984 a book was produced and edited by Watt et al., called 'Children at risk for schizophrenia'. In that book all the major high-risk studies were reported, including their findings up to that time. The book was a result of a conference held in 1972 in Dorado Beach, on children at risk for schizophrenia. As a result of that conference a

Consortium of risk research groups was established. The book was a product of the consortium. In all 12 research groups were represented, many of the issues raised in the book are outlined in the discussion of HR studies above. Studies other than those appearing in the 1984 book appear in Table 1.2. Information regarding the details of each of the studies was compiled from a number of sources and the references for each study is given in the bibliography of high risk studies. Numerous reviews of various aspects of the research have been published along the way.

Table 1.2. Summary of the First Generation High Risk projects; Design and Methods and Aims

Principal Investigators	Title	Aims	Design	Risk	Diagnosis	Control	Sociodemographic characteristics
Anthony and Worland	St Louis High Risk Project	To investigate the effects of psychosis on the child. The study had a clinical focus with the investigation of experimental, cognitive, perceptual, communication and psychosocial factors. Environmental focus.	Longitudinal design Began 1966 Children aged 6-12 years at intake Followed up ages 17 to mid 30's.	Offspring of patients with schizophrenia (n=100), manic depression (n=60)	DSM-II, later re-diagnosis to DSM III	Offspring of parents with physical illness (n=78; mainly TB) Normal controls (n=130)	Families were intact and located through psychiatric hospital. Mixed race, social class, and gender.
Erlenmeyer-Kimling	New York High Risk Study	To examine and compare groups of high-risk children to low risk children on; -neurological -psychophysiological -attention/distractibility -social interaction -behavioural, developmental and environmental changes, -anthropometrical measures Genetic orientation	Longitudinal Prospective study Began in 1971 Followed up at mean ages 9.5, 12, 15.5-16, 21	Sample A Offspring of schizophrenic mothers (n=44), fathers (n=23), and dual mated (n=12). Sample B Offspring of schizophrenic mothers (n=25), fathers (n=12), and dual mated (n=8) Information on siblings from sample A (n=122) and sample B (n=86)	Sample A Some given conservative diagnosis given by psychiatrist and some RDC Sample B RDC	Sample A Normal controls from the school system. Age, sex, and SEG matched (n=100), offspring of parents with other psychiatric problems (n=25) Sample B Normal controls found by a sampling firm matched on age, sex and SES (n=65), offspring of affective disorder parents (n=40).	Consecutive admissions to New York psychiatric facilities. White, English speaking, intact families, male and female offspring
Garmezy and Nuechterlein	Minnesota	To compare risk groups Three major areas of research interest; -(1) peer and teacher ratings and academic performance -(2) reaction time studies -(3) vigilance research -(4) incidental learning	Cross-sectional with different samples used in different studies. Three periods of sample recruitment for the specific studies in (1), (2), (3), and (4). Began in 1968 Children aged 9-17 years at recruitment 4-7 year follow-up 13-23	Offspring of schizophrenic mothers (n=(1)31, (2) 22, (3) and (4) 24). Offspring of depressed mothers and offspring of personality disordered mothers (n=20). Externalising children and internalising children Antisocial children (2), (3), (4) (n=16) hyperactive children from clinics (n=14)	Originally DSM II Re-diagnosed according to RDC in 1981-2 Hyperactive children (DSM-III)	Two controls, matched and random, located in the school system (n=67) matched on sex, age, reading vocabulary and comprehension scores, SES, peer evaluation, & sociometric status (2) (3) (4). Stratified controls (n=100) (2)	Mothers located through screening all female psychiatric admissions to several major facilities. All white with mothers aged 18-55.

Principal Investigators	Title	Aims	Design	Risk	Diagnosis	Control	Sociodemographic characteristics
Gallant and Grunebaum	Boston	Do children of psychotic mothers show cognitive deficits even in the preschool years? Are these deficits precursors, antecedents or predisposing to schizoph.? –relationship between child and maternal cognitive function -interaction between mothers and children	Cross sectional 15, 1 year olds 20, 3 year olds 10, 5 year olds 13, 6 year olds	Offspring of psychotic mothers (n=50) Offspring =68 16 of Schizophrenic 15 of schizoaffective 10 of depressed 4 of manic depression 5 borderline schizophrenia	Clinical, hospital diagnosis	50 mothers 68 children from the same backgrounds but no mental illness	White, intact families, mothers married, and at least 1 child less than 5 years.
McNeil and Kaij	The Swedish High Risk Study	-Look at OCs in psychotic mothers -Maternal attitudes -Mother child interactions -Physical health -Temperament -Foetal and infant ANS measures To compare risk groups on the above measures	Longitudinal prospective study Began 1973 -from birth sampled over 4-5 years Followed up at 3, 14 days, 4, 8, and 12 months, 6 years and latest follow up underway currently	Schizophrenia (n=29) Schizoaffective (n=15) Affective (n=27) unspecified functional psychosis (UFS; n=12), UFS with schizotypal features (n=2) other with schizotypal features (n=2), labile personality (n=1)	RDC and Project criteria (European classification)	Controls (n=103) matched on maternal parity, maternal age, social class, marital status at pregnancy (1 died before birth, originally 104).	Index mothers located from prenatal clinic lists for women who had been admitted to a psychiatric hospital
Mednick and Schulsinger	Copenhagen High Risk Study, Denmark	Children of mothers with schizophrenia compared to controls on; -clinical interviews -midwife reports -school performance -neuropsychology -psychphysiology; GSRs and EMGs.	Longitudinal prospective study Age range 9-20 years, mean age 15.7 Began 1962 Follow-up 1972, 1980, 1983, 1989	Offspring of schizophrenic mothers (n=207)	"would be diagnosed as severe in Europe and America" Later fathers were diagnosed	Controls with no immediate family member hospitalised with mental illness. Matched to index on age, sex, education, fathers occupation, urban/rural residence, and family structure	Source of subjects was the Danish Psychiatric Case Register
Weintraub and Neale	The Stonybrook High Risk Project	Adjustment of children of schizophrenic parents. -to identify precursor patterns -environmental stressors/protective patterns -psychological functioning in parents -family environment	Cross-sectional and longitudinal prospective Began 1971 Two groups; 6-10year olds and 11-15 year olds 3 year follow-up and again at 18 in young adulthood.	Offspring of schizophrenic parents (n=80), offspring of unipolar depression (n=154), offspring of bi-polar patients (n=134)	Detailed diagnostic assessment comparing well to both DSM II and DSM III	2 normal control groups (n=176) Classroom controls matched for gender; and a family control matched on age sex, race, social class, and IQ Both controls from the same class as the index subject	All new psychiatric admissions with school aged children at any o f 4 local inpatient facilities were screened

Principal Investigators	Title	Aims	Design	Risk	Diagnosis	Control	Sociodemographic characteristics
Weintraub and Neale cont.		-child adjustment -early signs; cognitive slippage, attention deficits, clinical symptoms					
Sameroff and Zax	Rochester Longitudinal study	Neonatal factor in serious mental disorder -to investigate early development of children at risk for later mental disorders due to mother mental illness -Maternal interviews, child scales, psychology, observation and teaching style -psychophysiology; EEG	Longitudinal prospective study Prenatal recruitment Began 1970 seen at birth, at 4, 12, 30, and 48 months Followed-up at 13	Schizophrenic (n=29), neurotic depressed (n=58), and personality disordered patients (n=40) identified through prenatal records compared to psychiatric case register	DSM II, some later re-diagnosed to DSM III	Offspring of a stratified sample of pregnant women not on the case register (n=57) Matched for age, race, marital status, SEG, maternal education, gender and parity	Women who were to deliver at a local hospital were checked against a psychiatric case register.
Schacter	Reactivity of neonates of schizohrenic parents	-Cross sectional study of newborn offspring of schizophrenic parents compared to controls -follow-up of other risk factors including; psychophysiology measures, OCs, videos	Cross-sectional with partial follow up at 18 months	Offspring of definite schizophrenics (n=22) offspring of schizophrenics of low certainty (n=25)	Judgement of 2 psychiatrists using the current and past psychopathology scale (Capps; Spitzer and Endicott, 1969)	Offspring of non schizophrenic (n=64)	Mothers mean age was 21.5 in an impoverished sample
Goldstein and Rodnick	UCLA Family project	Coping behaviour in schizophrenia. Measures of -Communication deviance -Expressed emotion -Affective style	Longitudinal Began 1964 Average age of adolescents =16 5-year follow-up ages 19-24 and 15-year follow-up 29-34.	1. Aggressive antisocial 2. Active family conflict 3. Passive negative 4. Withdrawn, socially isolated A total of 65 families	RDC and Borderline syndrome criteria	Each group served as a comparison to the others	UCLS psychology clinics
Rosenthal, Nagler, Kugelmass, Marcus	Israeli High Risk Project	"Neurological and physiological characteristics of the children of schizophrenic parents" -effect of being reared in a Kibbutz versus being reared at home on genetic risk for schizophrenia	Longitudinal prospective Began in 1965 Identified at average 11 (range 8.1 – 14.8) Evaluated at 11, 16, 26, and 31 years	Children of schizophrenic parents reared in a Kibbutz (n=25) Children of schizophrenic parents reared at home (n=25).	Diagnosis of schizophrenia or any sub group of schizophrenia, with several hospitalisations, and at least 3 classical signs	Children of those not at genetic risk for schizophrenia reared in a Kibbutz (n=25) Children of those not at genetic risk for schizophrenia reared at home in a town (n=25)	Sample IQ and SES were high on average, and predominantly middle class intact families

Principal Investigators	Title	Aims	Design	Risk	Diagnosis	Control	Sociodemographic characteristics
Rosenthal et al., continued		clinical assessment -psychomotor/ - psychometric tests -neurological exam -psychophysiology -sociometric measures			Later re-diagnosed to DSM-III-R	Matched on education, age, race, family size, parent's educational level, and parental cultural level.	
Wynne and Baldwin	University of Rochester Family Study	"Children and families vulnerable to schizophrenia" -To identify the diverse patterns of psychosocial competence, adaptation and biologic function of children at high v's low genetic risk for schizophrenia -relate these to parent symptoms and school and family factors -Follow development -Clinical, psychological and psychophysiology measures	Cross sectional with developmental follow up Began in 1972 Three cross-sectional groups studies; -ages 4.7. and 10 with follow up at ages 7, 10, and 13	Male off spring of schizophrenics (n=15), psychotic affective (60) patients	DSM-II DSM-III	Male off spring of non-psychotic, neurotic depressives (n=63) Groups matched on race, social class, age, language, family status, current illness status	The groups were all white, English speaking, social class III and IV (II if necessary), aged 10 or younger, family intact and 3 months since last hospitalisation
Mednick, Venables, Schulsinger, Dalens, Van Ousen	Martian Project	A controlled study of primary prevention -examine a normal population with ANS tests to try to detect those at risk for schizophrenia on this basis and explore possible intervention -Psychophysiological measures, behavioural Observation, cognitive measures, family interview, medical exam and perinatal information	Longitudinal, cohort, follow-up and intervention study Began 1972 11 year follow-up	Birth cohort identified from vaccination records including all three year olds in 2 communities. Total of 1800 identified, 1796 useable. 200 children identified as having deviant psychophysiology 100 placed in a nursery and given good diet and quality teaching		100 of the 200 identified as having deviant psychophysiology remained in the community	Mauritian cohort sample
Asarnow	McMasters-Waterloo project, Ontario, Canada	Emphasis on attentional functioning in those genetically at risk for schizophrenia compared to	Longitudinal prospective Began 1972 5 year follow up	Offspring of mothers with schizophrenia, samples of foster children at biological risk but not	Hospital diagnosis of schizophrenia including the requirement of 1 year in hospital of 3	Low genetic risk foster group (n=9). Randomly collected community control	Hospital admissions and community sample.

Principal Investigators	Title	Aims	Design	Risk	Diagnosis	Control	Sociodemographic characteristics
Asarnow continued		controls -cognitive assessment -neuropsychological assessments -psychiatric interview -assessment of environment	Ages 17 to 23	under the immediate social influence of the ill parent Tested at mean age 16 years away form the biological parent since mean age 9 (n=9)	admission, formal thought disorder, flattened affect, lack of volition, and psychomotor disorder	sample (n=10)	
Fish	New York Infant Development project	To identify characteristics and sequelae of neurointegrative disorder in infants at risk for schizophrenia Assessment of -physical growth -physiology -behaviour, -neurological maturation	Longitudinal prospective Began in 1952, Followed up, 9-10, 15-16, 18-19, 20-22, 26-27 some.	1952; offspring of mothers later diagnosed as schizophrenic (n=2) 1956; offspring of schizophrenic mothers (n=10). (of the 12 at risk; 6 adopted, 3 reared by granny and 3 at home but often in care)	DSM I	In 1952 offspring of non-psychotic mothers (n=12) In 1956 offspring of non-psychotic mothers (n=12)	Mainly low SES
Rolf	Vermont vulnerable child development project Epidemiology and intervention for children at risk	Concerned with; -contrasting developmental risks in pre-school children of psychiatrically hospitalised patients with controls -combining early identification of vulnerable children with preventative intervention	Longitudinal study Began in 1972 Aged 2 to 6 Mean age=4.4	24 parent-child pairs Parents aged 29-32 6 schizophrenic 18 depressive	DSM II	28 parent-sibling pairs Parents aged 29-32 No psychiatric contacts	Mean SC=III Mean maternal education=12years Controls had fewer broken h homes and fathers with higher education.
Marcus	Jerusalem Infant development study	To compare high and low risk infant groups Assessments -infant development scales -OCs -temperament Follow-up of school performance, social competence, cognitive function, behaviour assessments, neurological status, attentional function and motor behaviour	Developmental, longitudinal prospective study Began 1973 Studied at 3 and 14 day, and 4 and 8 months, 12 months and 10.3 years and at mean age 17 years	Subjects recruited nationwide from childcare centres Schizophrenic women who were pregnant were recruited (offspring, n=19), women with affective disorder (offspring, n=6) Intact families	DSM II Later diagnosed with RDC, DSM III	Women with no mental illness recruited in the same manner (offspring, n=19) Personality disorder and neurosis (offspring, n=14) Intact families	Middle and lower classes, mixed race, all families intact Subjects differ culturally and in terms of socio-economic class

Principal Investigators	Title	Aims	Design	Risk	Diagnosis	Control	Sociodemographic characteristics
Goodman	Emory university High-risk study, Atlanta, Georgia	Designed to provide descriptive data on the characteristics of young children of schizophrenic and depressed mothers Measures of: -IQ and social functioning, -neuropsychology -child rearing practices -linkages between parents diagnosis, child rearing environment, and child functioning -child temperament -OCs	Follow-up developmental study Began of 0-5 year olds Three testing times at one year intervals in 1981	Mothers with schizophrenia (n=71), mothers with depression (n=36), disturbed but no diagnosis (n=8)	DSM III	Well women (n=38)	98% black 90% single, low socio-economic status and a sample drawn from referral agencies, community mental health psychiatric clinics
Chapman	Study of college students with schizotypal features	Search for symptoms predictive of schizophrenia in the absence of a strong genetic component	25 month follow-up	Subjects scoring at least 2 standard deviations above the mean on a composite schizotypal questionnaire			
Hanson	Minnesota sample of a larger study	An attempt to specify individual who might be especially vulnerable to future schizophrenia Measures of; -Perinatal variables -physical growth -psychological -neurological	Prospective longitudinal design Assessed at 8 months 4 years, 7 years	Offspring of schizophrenic mothers (n=15) and schizophrenic fathers (n=14) (offspring n=33)	Records examined and consensus diagnosis given by 5 psychiatrists	Non schizophrenic psychosis, neurosis and depression (n=34; offspring n=36) Normal controls matched for social class, maternal age, maternal parity (n=33) and an unmatched group (n=33) from the same series	Sample form the Collaborative Study of Cerebral Palsy, Mental Retardation, other Neurological and sensory disorders in infancy and childhood; a prospective study conducted by the NCPP in collaboration with 12 university hospitals
Tienari	Finnish Adoption Study	To reassess genetic contributions to schizophrenia and to add measures of the adoptive family rearing environment, Measures of -communication deviance -attentional measures -smooth pursuit eye movements	Longitudinal design, Sometimes prospective as when first assessed some subjects had developed psychiatric illness Began 1962 5-7 year follow-up 12-17 year follow-up underway (Tienari, 1997)	Offspring of mothers with schizophrenia (n=155)	RDC DSM III-R diagnosis of schizophrenia or schizophrenia spectrum disorders	Offspring of control mothers (n=186) Subjects were individually matched	Case register based sample

1.7.1 General Review of High Risk studies

A more specific and focused review of the neuropsychological findings from the high-risk studies is given at the beginning of chapter 5 although some of the findings are discussed here in the general review for completeness. Asarnow (1988) reviewed the HR studies, with the aim of summarising what had been learned between 1952 and 1988, according to 5 life stages, or particular phases of development, in an effort to identify age-dependent variations in findings. The five life stages included:

1. Conception to Infancy (prenatal, perinatal, and infancy stages)
2. Early childhood
3. Middle childhood
4. Adolescence
5. Early adulthood.

The findings at each stage of development were subdivided into five categories, including neurointegrative functioning, social functioning, symptoms, general stressors, and family stressors. Not all areas could be addressed at all life stages.

Only findings where a significant difference was found between the HR and normal controls or psychiatric controls was reviewed, or if a variable was found to be associated with schizophrenic breakdown. Generally when HR subjects are compared with children of parents with other forms of psychiatric disorder, differences were not as great as when compared with children of normal subjects. Also the results come from different studies and not all will have covered the entire life span, and therefore trends may not be supported by longitudinal data on each cohort. The following is a summary of Table 2 of Asarnow's (1988) review, also the HR study acronym was taken from the same source.

1.7.1.1. Summary of the review of HR studies (Asarnow, 1988)

1. Neuroingegrative functioning Conception to Infancy	
Perinatal	Small for gestational age, low birth weight to length ratio (SW), Low birth weight (JIDS, RLS)
Infancy	Abnormal motor and sensory functioning (NY-F; D-OB; SW; JIDS; P; RLS). High or variable sensitivity to sensory stimulation (NY-F;SW;RLS). Abnormal growth patterns (NY-F; P). Short attention Span (C). Low IQ (E;RLS).
Early Childhood	Low reactivity (RLS). Poor gross and fine motor coordination (NCPP-H). Inconsistent variable performance on cognitive tests (NCPP-H; URCAFS).
Middle Childhood	Indices of neurological impairment (poor fine motor coordination, balance, sensory perceptual signs, delayed motor development; IS; NY-F; NY-E; NCPP-H; D-OB;NCPP-R). Attentional impairment under overload conditions (Minn; NY-E; SB). Variance scatter on intellectual tests (URCAFS).
Adolescence	Indices of neurological impairment (poor motor coordination, balance, sensory perceptual signs; IS; NY-E). Attention impairment under overload conditions (NY-E; M-W). Lower IQ (St.L; SB; C; IS). Drop in comprehension test score of the WISC-R between 10 and 15 years (NY-F). Inability to use low meaning cues on Referential Communication Task (SB). Greater reactivity on skin conductance measure (C).
Early adulthood	Poor performance on the WAIS Digit Span and Arithmetic subtests (IS). Enlarged brain ventricles (C).

2. Social Functioning	
Conception to Infancy	
Infancy	Difficult temperament (SW). Passive, low energy, quiet (C, NY-F). Inhibited, less spontaneous, imitative, expressive (B-G; P;E). Absence of fear of strangers (SW). Low communicative competence in mother-child interaction (E), Less social contact with mothers (SW).
Early Childhood	Depression (RLS). Angry and hostile dispositions (E). Low expressed negative affect (E). Anxiety (E). Schizoid behaviour i.e. emotionally flat, withdrawn, distractible, passive, irritable and negativistic (NCPP-H;NY-F). Low reactivity (RLS).
Middle Childhood	Poor affective control (emotional instability, aggressive, disruptive, hyperactive, impulsive; SB; NCPP-R; NCPP-H; NY-F; IS). Poor interpersonal relationships (Minn; SB-girls; NY-F; IS). Immature (fearful; inhibited; withdrawn; Minn.; NCPP-R;SB; MASS- girls only; NY-F; IS). Low cognitive and social competence (URCAFS; SB; IS). Poor attention (IS; SB).
Adolescence	Poor affective control (C; NY-E; St. L., UCLA; IS). Poor interpersonal relationships (C; NY-E; M-W; St. L., UCLA; IS). Poor school adjustment (C; NY-E; M-W; NY-F).
Early adulthood	Poor social adjustment (IS).

3. Symptoms	(*symptom outcome is more relevant, in relation to the diagnosis of adult mental health disorders, in the Cornblatt and Obuchowski 1997 review as studies were more evolved by this time and subjects had passed a through greater numbers of risk years*).

Symptoms continued	
Early childhood	More likely to receive a diagnosis of developmental disorder (E).
Middle childhood	Cognitive slippage disturbance (SB; St.L). Mixed internalizing-externalizing symptoms (SB). Attention deficit disorder-like syndrome (IS). More disturbed (SW; SB). More childhood disorders (NY-E).
Adolescence	Severe but non-psychotic behavioural disturbance (UCLA). Clinical maladjustment (SB). Cognitive Slippage (C).
Early Adulthood	High scores on perceptual aberration/magical ideation scales (W). Schizotypal symptoms and schizophrenia spectrum disorders (C; NY-E; F-T; IS). Higher rates of disturbance (F-T).

4. General Stressors	
Conception to infancy	
Perinatal	Delivery complications (RLS; P; C; F-W).
Early Childhood	Institutionalisation (Boys only –C)

5. Family Stressors	
Conception to infancy	
	Maternal stress (C;D-OB; F-W; P; SW; RLS; B-R)
Prenatal	Maternal risk-taking (RLS; SW; P; E)
Infancy	Nonoptimal maternal care (P; RLS; B-G; SW; E; NY-F). Anxious attachment to mother (SW).
Early childhood	Parental separation during first 5 years of life (boys only-C). Negative family environment (RLS; URCAFS; E; NY-F)
Middle childhood	Death of a parent (Mass.). Low rates of interaction or

5. Family Stressors continued	
	unbalanced interaction (URCAFS). Mothers show lax discipline (SB). Fathers unaccepting and uninvolved (SB). Poor family relationships (IS). Marital discord (SB).
	Child shows performance deficits under conditions of response contingent nonneutral social reinforcement by mother (URCAFS). Negative family environment (NY-F; SB). Parental communication deviance (UCLA).
Adolescence	Negative family environment (F-T; UCLA; NY-F; SB from adolescent perspective). Parental communication deviance (UCLA). Child shows failure to inhibit negative affect in family interaction (UCLA).
Early adulthood	Negative family environment (F-T)

KEY to Tables 1-5 above (Asarnow et al., 1988)

B-G	**Boston; Grunebaum.**
B-R	**Boston; Ragins.**
C	**Copenhagen High Risk Project**
D-OB	**Danish Prenatal Development project**
E	**Emory University**
F-W	**Finland; Wrede.**
F-T	**Finish Adoption Study**
IS	**Israeli High Risk Project**
JIDS	**Jerusalem Infant Development Study**
Mass.	**Watt in Massachusetts**
Minn.	**Garmezy et al., in Minnesota**
M-W	**McMaster-Waterloo**
NCPP-H	**National Institute of Neurological and Communicative Diseases and Stroke Perinatal Project; Hanson**
NCPP-R	**as above; Rieder and Nicols**
NY-E	**New York High Risk Project**
NY-F	**New York Infant Development Project**
P	**Pittsburg; Schachter, Ragins**
RLS	**University of Rochester longitudinal study**
SB	**Stony Brook High Risk Project**
St.L	**St. Louis High Risk Project**
SW	**Swedish High Risk Project**
UCLA	**UCLA family study**
URCAFS	**University of Rochester Child and Family Study**
W	**Wisconsin; Chapman and Chapman**

In 1987 Erlenmeyer-Kimling and Cornblatt published a paper summarising what had been learned up to that time. They had two main aims in that review, one was the description of background factors in the early lives of HR subjects and the other was the identification of biological variables that may be markers of the genetic liability to schizophrenic disorders. They concluded that in terms of background factors the results were confusing and conflicting, and that there is little evidence of specificity of the studied background factors to risk for schizophrenia, and indeed they may not be generalisable to most individuals who develop schizophrenia. They concluded that the results focusing on the biological variables were more promising. The results of the research focusing on the biological variables were summarised under the headings of attention and information processing (AIP), smooth pursuit eye movements (SPEM), neurological signs, electrodermal responding, event related potentials and ventricular size. Of these, certain AIP and SPEM dysfunctions showed substantial evidence of serving as biological markers. Certain AIP measures were thought to be promising in this regard, however, electrodermal responsivity was not. The other three categories presented uncertain or conflicting results.

Erlenmeyer-Kimling and Cornblatt (1987) concluded that no specific background factors had been identified, that are specific as precursors to schizophrenia e.g. pregnancy and birth factors, life events and social functioning in childhood, family relations and communication.

Erlenmeyer-Kimling and Cornblatt (1987) also pointed out that factor's which can be influenced by parents' mental health or behaviour cannot be generalised from studies of offspring to the majority of schizophrenics. The second major issue of risk research, as outlined by the authors, was the issue of identification of biological markers that reflect a genetic liability to schizophrenia or schizophrenia spectrum disorders, and is trait rather than state related. They noted that the investigation of biological markers in the

high-risk samples does not pose the same problem of lack of generalisability as does the investigation of the background factors as "there is no reason to believe that affected individuals with and without schizophrenic parents differ genetically or biologically"(Erlenmeyer-Kimling and Cornblatt, 1987, page 402).

The original review of Erlenmeyer-Kimling and Cornblatt (1987) was updated by Cornblatt and Obuchowski (1997). The focus this time, was on bio-behavioural markers, defined as subtle abnormalities in the neurocognitive domain (e.g. eye tracking dysfunction, and attentional impairment), referred to as bio-behavioural because the deficits detected are assumed to be intermediate between basic brain abnormalities and more complex clinical behaviours. The Erlenmeyer-Kimling and Cornblatt (1987) review is summarised in the following section.

A genetic component to the disorder was confirmed but there was no solid evidence for a link between environmental risk factors and specific behavioural outcomes. In terms of bio-behavioural and biological markers, impaired attention appeared to be the most widely supported candidate marker of the neurocognitive deficits investigated across studies (Erlenmeyer-Kimling and Cornblatt 1987; Hans and Marcus, 1991). Other neurocognitive markers appeared to have potential, but were less solidly supported. These included short-term recognition and recall memory and dysfunctions in the early stages of information processing, backward masking (Erlenmeyer-Kimling and Cornblatt, 1987). Eye movement dysfunctions (EMD) were another class of strong candidate markers. The evidence was mostly collected from adult first-degree relatives of patients with schizophrenia and other adult patient groups. Psychophysiological measures (Mednick and Schulsinger, 1968; Friedman et al., 1986) are not thought to be related to risk for schizophrenia. Neurological findings have been mixed, are inconsistent across HR studies, not specific to risk for schizophrenia and there was no evidence that neuromotor dysfunction was predictive of later clinical outcome (however early neurological dysfunction was noted in the developmental histories of those who later became schizophrenic in cohort studies, Jones et al., 1994, Done et al., 1994)

The following overview of the results of high-risk studies is a summary of Table 1 of the review by Erlenmeyer-Kimling and Cornblatt, (1987). There was no solid evidence for a link between descriptive background factors and risk for schizophrenia. The factors were evaluated according to whether the results indicated consistent deviance, were specific to risk for schizophrenia and were related to outcome. Generalisability was also considered. All results refer to offspring of schizophrenics in comparison with other samples, including parents, siblings, subjects selected by psychometric tests, subjects selected by biological tests, and twins. The factors included:

- pregnancy and birth history (Fish, 1984; Marcus et al., 1984; McNeil and Kaij, 1974, 1978; Mednick and Schulsinger 1968; Sameroff et al., 1984) for which the evidence was deemed inconsistent (i.e. no consistent pattern of deviance in the pregnancies and birth histories relating to the offspring at risk for schizophrenia compared to other groups), not specific for schizophrenia and their relation to outcome was unknown.
- life events (Bleuler, 1978; Mednick et al., 1978; Stainton, 1985), for which the results appear inconsistent, not specific for schizophrenia but related to outcome
- family relations and communications (Asarnow and Goldstein, 1986; Davis, 1985, Glish et al., 1982), results are consistent (i.e. there is typically greater deviance in these measures for the offspring at risk for schizophrenia compared to other groups), not specific but related to outcome.
- social functioning in childhood (Asarnow and Goldstein, 1986), the results were not consistent, specific or related to outcome
- social functioning in adolescence (Asarnow and Goldstein, 1986; Erlenmeyer-Kimling, 1985; Parnas et al., 1982), the results were consistent, not specific to schizophrenia but were related to outcome.

They also summarised the findings of the attention and information processing variables, again according to the consistency, specificity, and relationship of the variable to outcome.

These included:

- sustained attention measured using simple tasks (Review by Nuechterlein and Dawson, 1984, Rutschmann et al., 1986), the findings were mostly consistent, not specific to risk for schizophrenia or related to outcome
- sustained attention measured using complex tasks (Nuechterlein and Dawson, 1984; Cornblatt and Erlenmeyer-Kimling, 1985; Rutschmann et al., 1977, 1986), the findings were consistent, specific to schizophrenia and related to outcome
- selective attention (Nuechterlein and Dawson, 1984; Lifshitz et al., 1985), the results appear consistent, probably specific to schizophrenic and probably related to outcome
- short term memory recognition (Nuechterlein and Dawson, 1984) was found to be mostly consistent, but it is unknown if it is specific to risk for schizophrenia or related to outcome
- short-term memory recall (Nuechterlein and Dawson, 1984; Cornblatt and Erlenmeyer-Kimling, 1985, Lifshitz et al., 1985) again the results were mostly consistent, probably specific to risk for schizophrenia, and probably related to outcome.
- early processing stages (Nuechterlein and Dawson, 1984; Harvey et al., 1985; Merrit and Balogh, 1984) and concept formation (Nuechterlein and Dawson, 1984; McConaghy, 1959; Phillips et al., 1965) both have shown mostly consistent results, however the specificity to risk for schizophrenia and relationship to outcome was not shown.
- response readiness, the results have been inconsistent, not related specifically to risk for schizophrenia, or to outcome for either simple tasks (Nuechterlein and Dawson, 1984; Erlenmeyer-Kimling et al., 1982) or complex tasks (Nuechterlein and Dawson, 1984).
- smooth pursuit eye movement deficits have been consistently found in many samples, including offspring of schizophrenic parents, siblings, parents, twins and subjects selected by psychometric testing. The results are thought to be specific to

risk for schizophrenia, but the relationship to outcome was not proven (Holzman et al., 1984; Iacono, 1985; Siever, 1985)

- neuromotor dysfunction in infancy has been reported in offspring but not consistently, the results are not specific to risk for schizophrenia and the relationship to outcome was not confirmed (Erlenmeyer-Kimling and Cornblatt, 1984; Nuechterlein, 1986)
- neuromotor dysfunction in childhood has been consistently reported but it was not found to be specific to risk for schizophrenia, relationship to outcome was not confirmed (Erlenmeyer-Kimling and Cornblatt, 1984; Nuechterlein, 1986).
- electrodermal responsivity both hyper-responsivity (Erlenmeyer-Kimling et al., 1985; Kugelmass et al., 1985) and hypo-responsivity (Iacono, 1985). The findings were not consistent, or specific to risk, and probably not related to outcome.
- deficits in event related potentials have been investigated. Late positive components were investigated but yielded inconsistent results and were not found to be related to risk for schizophrenia specifically and were related to outcome (Iacono, 1985; Friedman et al., 1986; Josiassen et al., 1985; Saitoh et al., 1984; Simons et al., 1982)
- one study investigated the early positive components in siblings and parents and the specificity to risk for schizophrenia , and relationship to outcome is unknown, (Freedman et al., 1983; Siegel et al., 1984).
- ventricular enlargement was investigated in some imaging studies and the results have mostly been consistent but the specificity to risk for schizophrenia and the relationship to outcome are not known (DeLisi et al., 1986).

Erlenmeyer-Kimling and Cornblatt (1987) outlined 5 reasons why they believed the full potential of HR research had not been realised by that time.

1 The issue of power, most sample sizes have been relatively small. Each HR sample is probably an admixture of subgroups at risk for different genetic entities given that schizophrenia is genetically heterogeneous.

2 Diagnostic criteria were not standardized until after most HR studies were already underway.

3 Insufficient efforts were made to replicate assessments of the same domains of functioning let alone specific measures of such functions across studies, so many of the above variables have only been examined in a few samples.

4 Few samples have been followed up to determine whether dysfunction observed in given domains is frequently related to schizophrenic outcomes.

5 Control subjects at risk for other psychiatric disorders frequently have not been included, so the question of specificity to schizophrenia in regard to impairment cannot be addressed in many studies.

In 1997 Cornblatt and Obuchowski presented an update of the original findings presented in the earlier reviews. In the 1997 review Cornblatt and Obuchowski noted that 5 of the HR studies were still ongoing and had been conducted for a sufficient follow-up period to report adult clinical outcome. These studies included the New York Infant Development study (NYIDS), the Copenhagen HR project (CHRP), the Israeli HR study (IHRS), the Finnish Adoptive Family Study (FAFS), and the New York HR project (NYHRP). The Swedish HR sample is currently being followed up (McNeil, personal communication).

The clinical outcome of these five studies in terms of the rates of schizophrenia and psychosis is shown in Table 1.3

Table 1.3. The diagnostic outcome in the first generation HR studies

Study	Reference	Schizophrenia	Total psychosis
NYIHRS	Fish (1977)	8.0%	
CHRP	Parnas et al. (1993)	16.2%	20%
IHRP	Ingraham et al., (1995)	8.0 %	32.8% (24.8% affective disorder)
FAFS	Tienari et al., (1994)	5.2%	7.8%
NYHRP	Erlenmeyer-Kimling et al., (1995)	11.1%	18.6%

Also the findings of the first generation of high-risk studies tend to support the view that non-psychotic spectrum disorders aggregate in the families of schizophrenic probands and are therefore more likely to be less severe expressions of the schizophrenic illness (Cornblatt and Obuchowski, 1997, McGuffin et al., 1994).

Environmental risk factors

Environmental risk factors have not conclusively been identified. Family dysfunction, disturbed rearing environment, and obstetric complications (OCs) in the high-risk samples have not been confirmed, but interesting interactions have been noted (Cannon and Mednick, 1993; Wahlberg et al., 1997).

Neurological deficits

Fish et al., (1992), presented a re-analysis of previously published evaluations of infant motor disorder from 8 prospective studies and claimed that all show some evidence of gross motor delays in gross motor development in HR infants in the 1st two years of life (Marcus et al., 1987). There is also some evidence of disrupted motor development in those who later developed schizophrenia (Walker and Lewine, 1990; Jones et al., 1994; Done et al., 1994). A recent update of the Jerusalem Infant Development study (Hans et al., 1999), found that the offspring of parents with a diagnosis of schizophrenia who had developed schizophrenia spectrum disorders by adolescence (n=4) had a poorer pattern of neurointegrative functioning across developmental periods. This poor neurointegrative functioning was more apparent generally in the offspring of parents with schizophrenia especially males.

Attentional dysfunction.

Attentional dysfunction continued to stand out as one of the strongest candidate markers of a susceptibility to schizophrenia (Cornblatt and Keilp, 1994; Cornblatt et al., 1996). In the Israeli HRS and the NYHRP, attentional deficits were detected in childhood and found to predict later clinical disturbances in subjects at risk for schizophrenia (Cornblatt and Erlenmeyer-Kimling, 1985; Cornblatt and Keilp, 1994; Mirsky et al., 1995). Recent work suggests that the attentional trait is most likely a marker of the

biological susceptibility rather than the psychotic illness since childhood attentional deficits have been found to primarily predict schizotypal features in non-psychotic adults (Cornblatt and Keilp, 1994).

Neurocognitive dysfunctions.

Data from the NYHRP suggested that childhood deficits in working memory measured at mean ages 9.5, and 15 were relatively accurate predictors of the high-risk subjects who later developed schizophrenia related psychosis (Erlenmeyer-Kimling et al., 1996).

Eye movement dysfunction (EMDs)

Marker status has been derived from the evidence that EMDs are genetically transmitted biologically based and specific to schizophrenia (Levy et al., 1994). Eye tracking has not been studied in at risk children or adolescents, determination of the predictor potential of EMSs awaits more systematic investigation.

Psychophysiological variables.

Results are still not very convincing despite some interesting findings of interaction in the CHRP (Cannon and Mednick, 1993; Cannon et al., 1994).

Very little has been proven about the conditions or factors in the environment that are thought to escalate the susceptibility into full psychosis. Potential bio-behavioural markers impaired attention and eye movement dysfunction are leading contenders. Attentional impairment, under overload conditions, was found in middle childhood in the Minnesota study of Garmezy and Nuechterlein, in the NYHRS, and the Stony Brook project and in adolescence in the NYHRS and the McMasters Waterloo sample. Working memory appears to have marker potential however in the case of eye movements and working memory dysfunction, predictor validity has not been established. Abnormal motor development in infancy appears to be gaining evidence as a predictor.

1.8. Summary of the High Risk literature

Most of the findings reported by the 1st generation of studies (still ongoing) while interesting and very important, have not led to a definitive or even consistent, probable formula or mechanism to describe the later development of schizophrenia or psychotic symptoms in all of the subject who have developed them. Not all have attention deficits as children, not all have low IQ, and not all have neurointegrative deficits as children. The ideas of Hanson and colleagues (Hanson et al., 1990) return quite poignantly, that it is very difficult, if not impossible to predict along the line of synthesis (Freud, 1955), the outcome of schizophrenia in subjects from childhood behaviour as not all disturbed children develop into disturbed adults. The possibility of the non-linearity of development must be kept in mind, not to do so would be naïve. One evident problem is that of biological heterogeneity (Garver, 1987) and the need to be able to distinguish the HR subjects truly at risk by virtue of having the genotype from those who do not.

1.9 Bibliography of High-risk studies

The following list of reference was compiled using three main databases, Medline using the search engine, PubMed, and BIDS EMBASE through OVID, and PsycInfo. Medline, incorporates articles from 1966 to date. BIDS EMBASE covers from 1980 to date, and PsycInfo covers the years from 1967 onwards. Only PsycInfo includes book chapters. Literature searches were conducted on the name of the high-risk project, and also on the investigators name as authors. All publications relevant to the high-risk studies were selected for this bibliography. It is not a systematic review, but it was intended to include all articles published from the studies and appearing in the above databases, and also any relevant book chapters. The list of book chapters is not exhaustive. This was thought to be a necessary part of describing the high-risk studies, also to try to create a coherent framework to track a broad and sprawling literature, and for future reference. The reference list follows the format of Table 1.2. (The full bibliography is presented separately at the end of the thesis after the complete thesis bibliography).

Comprehensive and general reviews of the high-risk studies;
Anthony,1982, 1987a, 1987b; Asarnow, 1988; Asarnow and Goldstein, 1986; Cornblatt and Keilp, 1994; Cornblatt and Obuchowski, 1997; Cornblatt et al., 1996; Erlenmeyer-Kimling 1987; Erlenmeyer-Kimling and Cornblatt, 1987; Fish, 1975; Friedman and Squires-Wheeler, 1994; Garmezy, 1974a and 1974b; Glish et al., 1982; Goldstein, 1988; Hanson, 1990; Kremen et al., 1994; Lendingham 1990; Lewine et al., 1984; Lewine, 1984; Mednick and McNeil, 1968; Mednick et al., 1978; Nuechterlein et al., 1989, 1998; Nuechterlein and Dawson, 1994; Richters and Weintraub, 1990; Tienari and Wynne, 1994; Venables, 1977, 1993; Watt, 1986; Watt and Saiz, 1991; Wynne, 1984.

St Louis High Risk Project.
(Anthony, E.J., 1968, 1969, 1971, 1975, 1977, Anthony, B.J. 1978a, 1978b, Beck and Worland, 1983; Garmezy, 1974b; Janes et al., 1983, 1984; Shabad et al., 1979; Worland 1979a, 1979b; Worland et al., 1979, 1982, 1984a, 1984b, 1984c, 1987; Worland and Hesslebrook, 1980)

New York High Risk Project
(Amminger et al., 1999; Cornblatt and Erlenmeyer-Kimling, 1984, 1985; Cornblatt et al., 1989, 1992, 1996, 1999, Dworkin et al., 1990, 1991, 1993, 1994, Erlenmeyer-Kimling et al., 1980, 1982, 1983, 1984a, 1984b, 1985, 1989, 1990, 1991, 1993, 1995, 1997, 1998; Erlenmeyer-Kimling and Cornblatt, 1978, 1984, 1987, 1987,1992, Erlenmeyer-Kimling 1975; Freedman et al., 1998, Friedman et al., 1982, 1984, 1986, 1988, Garmezy, 1974b; Moldin et al., 1987a, 1987b, 1990a, 1990b, 1994; Ott et al., 1998; Rosenberg et al., 1997, Rutschmann et al., 1977, 1980, 1986; Squires-Wheeler et al., 1989, 1993; Watt et al., 1984, Winters, 1991).

Minnesota Cross-Sectional Studies
(Driscoll, 1984; Garmezy, 1973, 1974b, 1975a, 1975b, 1978, 1987; Garmezy and Devine, 1984; Masten et al., 1999; Nuechterlein et al., 1989, 1990; Nuechterlein 1983, 1984b, 1984b; Phipps-Yonas, 1984)

Boston; Grunebaum and Gallant
(Cohler et al., 1975, 1977; Cohler and Grunebaum, 1982; Gamer et al., 1976, 1977; Garmezy, 1974b; Grunebaum et al., 1974, 1975, 1978; Kaufmann et al., 1979; Herman et al., 1977).

Swedish High Risk Study
(Garmezy, 1974b; McNeil, 1986; McNeil and Kaij, 1974, 1987; NcNeil et al., 1974, 1983a, 1983b, 1984a, 1984b, 1984c, 1984d, 1985a; Näslund et al., 1984a, 1984b, 1984c, 1985; Persson-Blennow et al., 1984, 1986).

Copenhagen High Risk Project
(Burman et al., 1987; Carter et al., 1999; Cudeck et al., 1984; Cannon and Mednick, 1993; Cannon et al., 1988, 1989, 1990, 1990, 1992, 1993, 1994; Dykes, 1992; Erel et al., 1991; Garmezy, 1974b; Griffith et al., 1980; Higgins et al., 1997; Hollister et al., 1994; Itil et al., 1974; John et al., 1982; Jorgensen et al., 1987; Jorgensen and Parnas, 1990; Kirkegaard-Sorensen et al., 1975; LaFosse et al., 1994; Machon et al., 1983, 1987, Mednick B.R., 1973; Mednick S.A., 1966, 1970, 1971; Mednick et al., 1971, 1973, 1987, 1984; Mednick and Witkin-Lanoil, 1977; Mirdal et al., 1974; Olin et al., 1995, 1997,1998, Orvaschel et al., 1979; Parnas, 1985, 1986, 1988; Parnas et al., 1982a, 1982b, 1985, 1988, 1993; Parnas and Jorgensen, 1989; Parnas and Teasdale, 1987; Parnas and Schulsinger, 1986; Schulsinger et al., 1984; Schulsinger, 1976; Silverton et al., 1985, 1988a, 1988b, 1988c, 1983; Silverton and Mednick, 1984; Talovic et al., 1980; Tykra et al., 1995; Venables, 1993; Walker et al., 1981a, 1981b; Zorilla et al., 1997).

The Stonybrook High Risk Project
(Emery et al., 1982; Garmezy, 1974b; Harvey, 1991; Harvey et al., 1981, 1982, 1985; Neale et al., 1984; Neale and Harvey, 1985; Neale and Weintraub, 1975; Oltmanns et al., 1978; Weintraub 1987; Weintraub et al., 1975, 1978; Weintraub and Neale, 1984a, 1984b; Winters et al., 1981)

Rochester Longitudinal Study
(Garmezy, 1974b; Sameroff et al., 1982, 1984, 1987, 1993; Sameroff and Seifer, 1983, 1990, Sameroff and Zax, 1973; Seifer and Sameroff, 1987, Seifer et al., 1992; Zax et al., 1977)

Pittsburg: Schachter and Ragins
(Garmezy, 1974b; Ragins et al., 1975; Rubins et al., 1979; Schachter et al., 1977)

UCLA Family Project
(Alkire et al., 1971; Doane and Lewis, 1984; Doane et al., 1981a, 1981b; Garmezy, 1974b, Goldstein, 1985, 1987; Goldstein et al., 1968, 1970a, 1070b; Jones et al., 1977; Rodnick et al., 1984).

Israeli High Risk Project
(Frenkel et al., 1995; Garmezy, 1974b; Ingraham et al., 1995; Kaffman, 1986; Kugelmass, 1995, Marcus et al., 1987, 1989; Mirsky, 1986; Mirsky et al., 1985, 1995a, 1995b; Nagler, 1985, Nagler and Mirsky, 1985; Rabin, 1986; Silberman et al., 1985a 1985b; Sohlberg, 1985)

University of Rochester Child and Family Study
(Baldwin et al., 1984; Cole et al., 1984; Fisher et al., 1984, 1987; Garmezy, 1974b; Greenwald and Harder, 1994; Harder and Greenwald, 1992; Jones et al., 1984; Klein and Salzman, 1978, 1981, 1984; Kokes et al., 1984; Munson et al., 1984; Prentky et al., 1981; Salzman and Klein, 1978; Strauss et al., 1979; Wichstrom et al., 1993a, 1993b, 1996a, 1996b; Wynne, 1984; Wynne et al., 1987; Yu et al., 1984)

Mauritian Project
NOTE: Subjects in the Mauritian project were designated 'at risk' on the basis of their deviant physiological responses, not by genetic risk. This project was not successful as a high-risk for schizophrenia project and appears to have become a successful study of precursors to criminality. The project, with references to the criminality literature, is included here for completeness as at its outset it appeared to have the potential to be a successful high-risk for schizophrenia project.

(Bell et al., 1975; Garmezy, 1974b; Mednick et al., 1984; Raine and Venables, 1984, Raine et al., 1995, 1997, 1998; Scarpa et al., 1995, 1997; Schulsinger et al., 1975; Venables, 1984,1989, 1996, 1997, 1998).

McMasters Waterloo
(Asarnow, 1984; Asarnow et al., 1977, 1979, 1985; McCrimmon et al., 1980; Steffy et al., 1984)

New York Infant Development Study
(Fish, 1957, 1959, 1960, 1971, 1975, 1976, 1977, 1982, 1984, 1986, 1987; Fish and Alpert, 1962, 1963; Fish and Dixon, 1978, Fish and Hagin, 1972, 1973, Fish et al., 1965, 1966, 1992)

Vermont Vulnerable Child Development Project
(Fischer et al., 1984;Garmezy, 1974b; Rolf, 1972, 1976; Rolf and Garmezy, 1974; Rolf and Hasazi, 1977; Rolf et al., 1981, 1982, 1984)

Jerusalem Infant Development Study
(Auerbach et al., 1993; Bernstein et al., 1986; Fish et al., 1992; Hans and Marcus, 1991; Hans et al., 1992, 1999; Marcus, 1982, Marcus et al., 1981, 1985a, 1985b, 1985c, 1984, 1987, 1989, 1993)

Emory University High Risk Study
(Goodman, 1984a, 1984b, 1984c, 1987, 1991)

Study of Psychosis Proneness: Chapman and Chapman
(Chapman and Chapman, 1987; Chapman et al., 1994)

National Institute of Neurological and Communicative Diseases and Stroke Perinatal Project: Hanson et al.,
(Garmezy, 1974b; Hanson et al., 1976; 1990)

Finnish Adoption study
(Tienari, 1992, 1991; Tienari et al., 1983, 1985a, 1985b, 1987a, 1987b, 1987, 1989, 1990, 1994; Wahlberg et al., 1997).

Other risk studies described in the Garmezy 1974b paper:

A). Studies where no references could be found in EMBASE, PsycInfo, or MEDLINE.

Zira Defries (New York, USA)

' Clinical evaluation of coping styles in children'

Kantor D (Cambridge Mass., USA)

' A study in vivo of disturbed and normal families'

Kringlen, E (Oslo, Norway)

'Children of 2 psychotic parents' study intended.

Miller D (San Fransico, USA)

'Mental patients as parents'.

B). Studies where references were found;

Watt, N (Mass., USA)

'Patterns of personality development' a follow back study.

(Lewine et al., 1978a, 1978b; Prentky, 1980;Watt, 1972, 1978; Watt et al., 1970; Watt and Lubensky, 1976)

Offord D (Penn., USA)

'Childhood antecedents of adult schizophrenia' a follow back study.

(Offord, 1974, Offord and Cross, 1971; Jones et al., 1975).

Pollack, M (New York, USA)

'Schizophrenics and non-schizophrenics and their siblings' a retrospective study.

(Pollack et al., 1966, 1969a, 1969b).

Other Studies included in the review by Asarnow (1988):

National Institute of Neurological and Communicative Disease and Stroke Perinatal project: Rieder and Nicol
(Rieder et al., 1975, 1977, Rieder and Nicol, 1979)

Pregnancy and delivery complications in the births of an unselected series of Finnish children with schizophrenic mothers:
Wrede in Finland
(Wrede et al., 1980, 1984).

CHAPTER TWO: THE EDINBURGH HIGH RISK PROJECT

2.1. The Edinburgh High Risk Project: description, and methodology.

The Edinburgh High Risk Project was set up in 1994, and is funded by the Medical Research Council. The grant holders include Professor Eve Johnstone, Professor of Psychiatry and Consultant Psychiatrist, University of Edinburgh, Dr. David Owens, Reader in Psychiatry, University of Edinburgh, and Professor Jonathan Best, Consultant Neuroradiologist, University of Edinburgh. The project began in July 1994 and ran until July 1999 in its initial phase, however the group will be followed up for another 5 years in relation to a second programme grant. The study is based at the Department of Psychiatry, University of Edinburgh, with recruited participants from all over Scotland.

The original proposal stipulated that all participants should be aged between 16 and 24 years old at recruitment. Three different groups were to be recruited. Group one was to include individuals from high-risk families (where at least two other members suffer, or have suffered from a psychotic illness which is not unequivocally affective). Some were to come from High Density families (families that have multiply affected members). Group two was to include normal controls without a family history of psychotic illness in either first or second-degree relatives. Group three was to include people without a family history of psychotic illness who present with their first psychotic episode. The groups were followed up at 18 month intervals for 5 years or until they developed psychotic symptoms. Once recruited, at each assessment subjects received a detailed clinical assessment, structural brain imaging in the form of an MRI scan, and a detailed neuropsychological assessment battery. Also detailed demographic, obstetric, dermatoglyphic, and childhood behavioural information was collected.

The overall aims of the study

1. To determine the clinical, psychological, and neurological features and detailed brain structures which distinguish those members of high-risk families who develop schizophrenia from those who do not.

2. To compare the results from this group with other first episode cases of schizophrenia and with normal controls.

In this PhD thesis it will only be possible to address fully the second aim in detail as it is too early, and too few individuals have become ill as yet to make any definitive conclusions about the first.

The causes of schizophrenia remain unknown. The only confirmed risk factor for schizophrenia is having a family history for the disorder. The risk of developing the disorder for first-degree relatives of a schizophrenic proband is between 6 and 13 (Gottesman and Shields, 1982) times greater than that of the general population. For this reason it is useful to study individuals at high-risk for schizophrenia, to try to unfold the reasons why some develop schizophrenia and others remain well. In this population, due to the risk status, the numbers developing the disorder will be greater than in a comparable sized general population sample. High-risk research is not without its own problems, discussed in chapter one, but it provides a method of studying the onset and development of schizophrenia that would not be feasible in other samples. The Edinburgh High Risk Study (EHRS) was designed to follow young adults through an estimated 60% of their maximum risk period for developing schizophrenia, over a 5-year period. This design redresses some of the difficulties of other high-risk projects (Erlenmeyer-Kimling and Cornblatt, 1987). Recruitment in young adulthood prevents such high attrition rates from childhood to adulthood. The onset of schizophrenia most commonly occurs within this age group (Hafner and an der Heiden, 1997). The change from risk and prodromal state to florid illness is not clearly understood, opportunities to study it have been few, however it can be closely monitored in this investigation. It has the advantage of being a study of adult relatives of patients with schizophrenia as well as being a high-risk design, the full power of which can only be revealed in time. Differences between functional and behavioural patterns in childhood and adulthood preclude the generalisation of findings in children to adults. This is avoided in the EHRS.

2.2. Recruitment

The following were the steps taken to ensure that the approach to families was acceptable. Subjects were recruited principally by Dr. Ann Hodges, Dr. Elizabeth Grant, and Dr. Bobby Clafferty.

1. The case notes of patients known to the mental health care professionals (Consultant Psychiatrists, Registrars, and Nurses) were examined. In Edinburgh it was possible to use the Lothian Case Register to identify cases of schizophrenia, and the notes of those identified for the 3 years prior to 1994 were reviewed.
2. Possible families were identified. Those where the index patient with a schizophrenic illness had another like affected relative and also had well young relatives in the relevant 16 to 25 age group.
3. The Consultant or GP was contacted, in most cases there was liaison with the CPN, Social Worker or Key Worker, and permission was sought to approach the index patient.
4. An interview took place with the index patient asking permission to speak to the relevant young family members or their parents if the person was less than 18. The subject's GP was contacted at this stage to ensure that it was not a bad time to approach the family. Finally the subjects' aged between 16 and 24 were contacted and invited to take part in the project.

Information was given to the GP's and to the Participants explaining the project and their involvement in it.

2.3. Participants

Note on social class categorisation: The social class represents fathers' occupation at time of birth and was obtained from the birth registration forms for those born in Scotland, and by maternal interview where possible. Occupations were coded according to the classification of the Office of Population, Censuses and Surveys (1980).

2.3.1. High Risk Subjects

Recruitment was completed in December 1998. Subjects were recruited from around Scotland with the kind co-operation of the medical staff and families in each area. Ethical approval was sought and granted from the 10 of the 15 Health Boards in Scotland from which the subjects for the study were recruited (see figure 2.3.1 for geographical boundaries and total population estimates of each health board). The Health Boards included Lothian, Dumfries and Galloway, Lanarkshire, Tayside, Borders, Argyll and Clyde (including Paisley, Argyll and Bute, and Greenock subdivisions), Highland, Western Isles, Fife, and Forth Valley. In total 229 young people between the ages 16 and 25 were identified from around Scotland, came from families where at least two family members had a diagnosis of schizophrenia, and consented to enter the study. Recruitment of the first 100 is outlined in Hodges et al., 1999. The diagnoses were confirmed by Professor Johnstone using the OPCRIT programme (McGuffin et al., 1991). Subjects were recruited by scrutiny of the case notes of all schizophrenic patients know to the individual hospitals. Where it appeared that an individual patient had a close relative also affected, consent from the patient was sought to speak to a well relative. Details of the full family history were obtained from this person and in particular the possibility of there being close relatives aged 16-24 was explored. Permission was sought throughout from involved clinical teams and relevant medical practitioners. Young well family members were then approached, usually through the well adult relative. The approach was conducted with care and in practice it worked very well. It was a very labour intensive process involving the reading of thousands of case notes and many home visits to patients and their families. The profile of family history in the high-risk group is outlined in Table 2.3.1.

Of the total number identified 162 individuals actually took part in the research, representing 110 families. Of this 150 were scanned, 149 had neuropsychological assessments, 149 had clinical assessments. In total 140 individuals had the full protocol.

Table 2.3.1. Family history of psychosis among the High Risk group

Family relationship	High Risk group, n=162 n (%)
Mum/Dad and Sib	13 (8.0)
Mum (and other)	37 (22.8)
Dad (and other)	18 (11.1)
Two siblings	6 (3.7)
One sibling (and other)	32 (19.8)
Two 2nd degree relatives	56 (34.6)
Affected status of parents	
Mum (and other)	46 (28.4)
Dad (and other)	22 (13.6)

Of the 67 subjects who did not take part, 40 refused, 21 were not available at the time of recruitment, 6 never responded to contacts. The social and demographic structure of the high-risk group is given in Table 2.3.2.

Table 2.3.2. Demographic structure of the High-Risk Group.

n=162	Males (n=79)	Females (n=83)
Age structure	**Mean (s.d)** 21.20 (2.90)	**Mean (s.d)** 21.18 (3.06)
Social class at birth	**n (%)**	**n (%)**
Social class I & II	19 (24.1)	11 (13.3)
III & IV	44 (55.7)	43 (51.8)
V & VI	14 (17.7)	26 (31.3)
Unclassifiable	2 (2.5)	3 (3.6)
Health Board Region	n	n
Argyll & Clyde	20	21
Borders	2	0
Dumfries & Galloway	0	2
Fife	6	7
Forth Valley	4	4
Highland	2	1
Lothian	43	43
Tayside	0	5
Western Isles	0	2

Note on follow-up assessments: Because recruitment began at the time the study started and continued for 4.5 years, the length of time subjects had been recruited varied greatly and a large number were not eligible to attend for a second round of assessments, and fewer still were eligible for a third round of assessments.

Second round: Eighty high-risk subjects attended for a second round of assessments an average of two years after the original assessment. A further 29 subjects were eligible to attend (eighteen months since original assessment, and had not developed a psychotic illness during this time), but did not. Ten subjects agreed to take part, did not attend on the day and a subsequent time could not be arranged, in addition 9 HR subjects agreed to take part a second time but were too busy when contacted. It was hoped that these subjects could be assessed in the future. Only five subjects refused to take part a second time. At the time of the first assessment two of the subjects expressed a wish not to be contacted for follow-up.

Third round: 29 HR subjects returned for a third round of assessments.

2.3.2. Controls subjects

In total 35 normal controls were recruited. The young people in the control group had no known psychotic relatives but could have a second degree relative with other psychiatric illnesses e.g. alcohol dependency, eating disorders and Alzheimer's disease. Initially the control group was recruited from Edinburgh Youth Groups but as it became clear that many of the subjects would live far from Edinburgh frequently in rural areas the approach of recruitment from the social network of the subjects themselves was adopted. This allowed us to improve the matching for age and social class.

Of the 35 controls, all had scans, 34 had neuropsychological assessments, and 32 had clinical assessments. 32 subjects completed the protocol. The control group social and demographic characteristics are outlined in Table 2.3.3.

Second round: 22 control subjects returned to complete a second round of assessments on average two years after the first assessment. 11 more were eligible to return for assessments (more than eighteen months had elapsed since the first visit). Of these 11

subjects four were lost to follow-up due to moving from their original address, 2 were pregnant and decided it was not a good time for them, five were too busy but agreed in principle.

Third round: Four subjects returned for a third round of assessments.

Table 2.3.3. Demographic structure of the Control Group.

n=35	Males (n=17)	Females (n=19)
Age structure	**Mean (s.d)** 21.21 (2.34)	**Mean (s.d)** 21.12 (2.45)
Social class at birth	**n (%)**	**n (%)**
Social class I & II	8 (47.1)	3 (15.8)
III & IV	6 (35.3)	11 (57.9)
V & VI	3 (17.6)	3 (15.8)
Unclassifiable	0 (0)	2 (10.5)
Health Board Region	**n**	**n**
Argyll & Clyde	0	1
Fife	2	1
Lothian	16	15

2.3.3. First episode cases

Thirty seven cases of first episode schizophrenia were recruited. They were recruited from the Royal Edinburgh Hospital, and also from St. Johns Hospital in Livingston, West Lothian. 34 of these had scans, 29 had neuropsychological assessments, and 37 had clinical assessments. The first episode group social and demographic characteristics are outlined in Table 2.3.4. The first episode group were assessed once only. It should be noted that in general, the first episode group were symptomatic and on antipsychotic medication when assessed. More males were recruited to the first episode group (68%) compared to a more even gender distribution in the other groups. This was most likely because males typically experience their first episode of schizophrenia at a younger age than females and so more first episode males than females were available within the project age range of 16-25 years.

Table 2.3.4. Demographic structure of the First Episode group

n=37	Males (n=25)	Females (n=12)
Age structure	**Mean (s.d)**	**Mean (s.d)**
	20.76 (2.42)	23.44 (5.14)
Social class at birth	**n (%)**	**n (%)**
Social class I & II	5 (20.0)	5 (41.7)
III & IV	12 (48.0)	1 (8.3)
V & VI	2 (8.0)	1 (8.3)
Unclassifiable	6 (24.0)	5 (41.7)
Health Board Region	**n**	**n**
Lothian	25	12

Figure 2.3.1. Map of Scotland delineating the Health Board Areas and the estimated population of each.

Argyll and Clyde	(429,300)		Ayrshire & Arran	(376,500)	
Borders	(106,200)		Dumfries & Galloway	(147,300)	
Fife	(348,400)		Forth Valley	(275,600)	
Grampian	(528,400)		Greater Glasgow	(905,100)	
Highland	(208,600)		Lanarkshire	(561,600)	
Lothian	(772,000)		Orkney	(19,840)	
Shetland	(23,020)		Tayside	(392,400)	
Western Isles	(28,240)				

2.4. Subject assessments: Baseline

2.4.1. Neuropsychological assessments

Neuropsychological dysfunction has been reported in relatives of schizophrenia patients (e.g. Faraone et al., 1995; Toomey et al., 1998). Specific domains of neuropsychological dysfunction have been identified. The tests were organised according to general neuropsychological practice (Lezak, 1995) and in a manner similar to previous studies of adult relatives of patients with schizophrenia (Kremen et al., 1994). The test battery used in this study was designed to include tests which have been previously shown to differentiate subjects at high-risk for schizophrenia and controls (Kremen et al., 1994), tests which have shown differences between schizophrenia patients and controls, and tests which localise to parts of the brain which have been shown on imaging or other investigations to differ between schizophrenia patients and controls. The battery was designed to be repeatable and not so prolonged that compliance would be reduced. These are the preliminary findings of an ongoing study.

The Neuropsychological assessment battery included assessment of current and premorbid intellectual function, executive function psychomotor speed, mental control encoding, sustained attention, verbal ability and language, learning ability and memory, and a measure of lateral preference. A detailed description of the tests are presented in chapter three and outlined in chapter 3, Table 3.1.

2.4.2. Clinical assessments

The clinical assessments included the Present State Examination (PSE; Wing et al., 1974), the Schedule for Affective Disorders and Schizophrenia-Life time version (SADS-L; Endicott and Spitzer, 1978) and the Structured Inventory for Schizotypy (SIS; Kendler et al., 1989). The Rust Inventory for Schizotypal Cognitions (RISC; Rust, 1988) was also administered. Each subject filled out a life events questionnaire (Paykel et al., 1971). An examination of Neurological Soft Signs (Buchanan and Heinrichs, 1989) was conducted, and also an assessment of Minor Physical Anomalies (MPA's; Waldrop et al., 1968).

2.4.3. Social, Demographic Information

Demographic information was collected at the interview, including information on fathers' occupation, previous psychiatric contacts, substance abuse, and information regarding educational attainment and education history.

2.4.4. Obstetric information

In addition, permission to contact the Mother of each subject was requested in order to obtain a detailed obstetric history relating to the pregnancy and delivery. In addition mothers were asked to fill in the Childhood Behaviour Checklist (Achenbach, 1993) and to give signed consent to allow us to access the obstetric data held on computer at the Information and Statistics Division in Edinburgh, in the form of maternal discharge summaries and neonatal records. The purpose was to compare the maternal recall data with the contemporaneously collected information to assess the reliability of the former and the degree of concurrence between the two.

2.4.5. Dermatoglyphics

Finger and palm prints were taken from each subject, using an inkless method.

2.4.6. Brain imaging

Each subject underwent MRI scanning on a 1 tesla Siemens (Erlangen, Germany) Magnetom scanner. Midline sagittal localisation was followed by two sequences to image the whole brain. The first scan was a double spin echo sequence, which gave simultaneous proton density and T2 -weighted images (TR= 3565ms, TE=20 and 90ms, 31 contiguous 5 mm slices acquired in the Talairach plane, field of view 250mm), which were used to exclude any gross brain lesions. The second scan, for the volumetric analysis, was a three dimensional Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence consisting of an 180 degree inversion pulse followed by a Fast Low Angle Shot (FLASH) collection (flip angle 12^{o}, TR = 10ms, TE = 4ms, TI = 200 ms, relaxation delay time 500 ms, field of view 250mm) giving 128 contiguous 1.88 mm thick slices in the coronal plane orthogonal to the Talairach plane. Any inhomogeneity in the head coil was corrected for. Image processing was done on

the Sun Microsystems workstations using the software package "Analyze" (Mayo Foundation, Rochester, MN, USA) to outline neuroanatomical structures. Suheib Abukmeil, Julia Kestleman, and Heather Whalley carried out the volumetric image processing. Satisfactory interrater reliability was achieved (Whalley et al., 1999). The results of the brain imaging data for the first 100 subjects were described by Lawrie et al., (1999).

2.5. Subject assessment: Follow-up

2.5.1. Second Round Assessments

The first episode patient group were not assessed at follow up. Eighty high-risk subjects and 25 controls were seen for a second assessment, the remainder generally not having been in the project for long enough to be eligible for follow-up. Details of the neuropsychological assessments are given in Chapter 3, Table 3.2. An identical scan protocol was administered. Ten of the high-risk subjects refused a scan and 1 of the controls having not liked the experience first time round. At the second interview the clinical assessment included the PSE and the SIS. Also detailed information was requested in order to update our files on the subjects' current circumstances.

2.5.2. Third Round Assessments

Thirty high-risk subjects and 5 controls were seen for a third assessment. Third round neuropsychological assessments are shown in Chapter 3, Table 3.3. The scan protocol was again repeated. For the clinical assessment the PSE was conducted, also the detailed information sheet was filled in so the files could be updated.

2.6. Comparison of the groups with respect to socio-demographic characteristics

Demographic information was collected at each interview, including information on fathers' occupation, previous psychiatric contacts, substance abuse, and information regarding educational attainment and education history. Descriptions of the socio-demographic characteristic of the groups at each assessment are displayed in the following series of Tables. Statistical analyses were not conducted on the third round demographic data, as the numbers were too small for valid results to be obtained.

2.6.1. Social Class at origin

It was decided that social class at birth, defined by the occupation of the father and coded according to a standard classification system (OPCS) would be a suitable measure of social class. It removes as far as possible, factors relating to social decline due to illness that the family may have experienced after the birth of the subject. It also removed the problem of ill fathers moving away from the family structure over the life span of the subject, and not being in contact at the time of assessment. Birth registration information, which is held at New Register House in Edinburgh, was consulted to obtain information about father's occupation. This applied only to those born in Scotland. For those not born in Scotland, information about fathers occupation at the birth of the subject was obtained from the mothers, where possible, as part of the obstetrics questionnaire.

Social class of origin is displayed in Table 2.6.1. Statistical analyses was conducted using the Kruskal-Wallis non-parametric one way analysis of variance to investigate possible differences between the three group at baseline assessment in order to see if they were relatively well matched on this variable. Mann-Whitney U test was used to examine differences between the HR and control groups at second round assessments. No significant differences were found between the groups at baseline or second round.

Table 2.6.1. Distribution of social class of origin at each assessment

ROUND ONE	High Risk n (%) n=162	Controls n (%) n= 36	Patients n (%) n=37	Statistical analyses
Social Class of Origin				Kruskall-Wallis
1 and II	30 (18.5)	11 (30.6)	10 (27.0)	
III and IV	87 (53.7)	17 (47.2)	13 (35.1)	χ^2=2.69 p=0.26
V and VI	40 (24.7)	6 (16.7)	3 (8.1)	
Unclassifiable	5 (3.1)	2 (5.6)	11 (29.7)	
ROUND TWO	**High Risk n (%) n=80**	**Controls n (%) n= 22**		
Social Class of Origin				Mann-Whitney U
1 and II	22 (27.5)	10 (45.5)		
III and IV	42 (52.5)	9 (40.9)		Z=-1.52 p=0.13
V and VI	13 (16.2)	3 (13.6)		
Unclassifiable	3 (3.8)			
ROUND THREE	**High Risk n (%) n=29**	**Controls n (%) n= 4**		
Social Class of Origin				
1 and II	7 (24.0)	3 (75.0)		
III and IV	17 (58.6)	1 (25.0)		Numbers too
V and VI	4 (13.7)			small for
Unclassifiable	1 (3.4)			statistical analysis

2.6.2 Educational qualifications

Subjects were asked about their educational qualifications. Details of educational qualifications in the three groups are presented in Table 2.6.2. Overall there was a significant difference between the three groups in terms of educational qualifications. Mann-Whitney U tests were conducted to see if there were any differences between group pairs, as a means of post hoc evaluation of the Kruskal-Wallis test results. The high-risk and control groups did not significantly differ from each other (Z=-1.24, p=0.21). There was a trend for the HR group to have higher educational qualifications than the patient group (Z=-1.88, p=0.21), with the control group having significantly higher educational qualifications than the patient group (Z=-2.44, p=0.01). At the second round of assessments controls and HR subjects did not differ significantly in terms of education.

Table 2.6.2 Educational Qualifications of the high-risk, control, and 1st episode group at each assessment.

ROUND ONE	High Risk n (%) n=154	Controls n (%) n= 35	Patients n (%) n=33	
Left school before exams	14 (9.1)	1 (2.9)	6 (18.2)	Kruskal-Wallis
Sat leaving exam (O / Standard Grades/ Highers/A Levels)	54 (35)	10 (28.6)	14 (42.4)	
Cert. /diploma entry	28 (18.2)	5 (14.3)	3 (9.1)	χ^2=6.12 p=0.05
Degree/post grad entry	28 (18.2)	15 (42.9)	7 (21.2)	
Vocational Training	15 (9.7)	1 (2.9)	3 (9.1)	
Still at school	15 (9.7)	3 (8.6)	0	
ROUND TWO	**High Risk n (%) n=79**	**Controls n (%) n= 22**		
Left school before exams	4 (5.1)	1 (4.5)		Mann-Whitney
Sat leaving exam (O / Standard Grades/ Highers/A Levels)	23 (29.1)	5 (22.7)		
Cert. /diploma entry	17 (21.5)	3 (13.6)		Z=-0.76 p=0.44
Degree/post grad entry	28 (35.4)	12 (54.5)		
Vocational Training	7 (8.9)	1 (4.5)		
Still at school	0	0		
ROUND THREE	**High Risk n (%) n= 29**	**Controls n (%) n= 4**		
Left school before exams	2 (6.9)	0		Numbers too small for statistical test
Sat leaving exam (O / Standard Grades/ Highers/A Levels)	8 (27.6)	2 (50)		
Cert. /diploma entry	8 (27.6)	0		
Degree/post grad entry	9 (31)	2 (50)		
Vocational Training	2 (6.9)	0		
Still at school	0	0		

2.6.3. Education and employment status in the groups

The current education and employment status of the groups at baseline assessment is outlined in Table 2.6.3. Subjects were classified as employed, unemployed, or still in education. A chi-square analysis was conducted on the data. The groups were found to differ significantly overall. All groups were found to differ from each other. The adjusted standardised residuals (ASR's) are presented in the Table to indicate the significant differences. ASR's greater than $\pm$ 2 indicate a significant deviation from the expected proportion. Compared to the patient group, the HR group was significantly more often in employment. Compared to the other two groups

significantly more controls were still in education. There was a significant excess of patients in the unemployed category.

Table 2.6.3. Description of educational and employment status in the groups

ROUND ONE	High Risk, n (%) n= 155	Controls n (%) n= 35	Patients n (%) n=37	
% EMPLOYED	89 (57.4) ASR=3.4	16 (45.7)	8 (21.6) ASR=-3.7	
% UNEMPLOYED	27 (17.4) ASR=-3.3	3 (8.6) ASR=-2.3	24 (64.9) ASR=6.4	χ^2=47.47 P=0.00
% STILL IN EDUCATION	39 (25.2)	16 (45.7) ASR= 2.8	5 (13.5)	

2.6.4. Outline of family history

Family history of schizophrenia at each visit is presented in Table 2.6.4. No statistical analysis was conducted on this data; it was intended to be purely descriptive. To be defined as a control subjects could not have a positive family history of schizophrenia. The HR group was divided into those who had 2 or more second degree family members with a history of schizophrenia, those with one first degree relative and at least one second degree relative also affected, and those with at least two or more first degree relatives affected.

Table 2.6.4.Family history of schizophrenia, Control and High-risk groups

	Visit one n (%)	Visit two n (%)	Visit three n (%)
No family history (Control group)	36 (100)	22 (100)	4 (100)
Two or more 2nd degree	56 (34.57)	24 (29.63)	7 (24.14)
One 1st degree (and second degree)	87 (53.7)	50 (61.73)	21(77.78)
Two or more 1st degree	19 (11.73)	7 (8.64)	1 (3.45)

2.6.5. Age of subjects, gender, marital status and number of children

The age structure of the groups is outlined in Table 2.6.5. A one-way analysis of variance was conducted on the baseline data, and independent t-tests were conducted on the follow-up data. The groups did not differ significantly in terms of age at any time. Similarly there was no significant difference across the groups in the distribution of gender, or marital status. The patient group did not have any children at all. There was no significant difference between the high-risk and control groups in terms of the number of the children they had.

Table 2.6.5. Age of subjects Gender, marital status and number of children

Age	**High Risk group**	**Control group**	**1st Episode group**	**F/t**	**P**
Visit one	*n=162*	*n=36*	*n=37*		
Mean Age (sd)	21.19 (2.97)	21.17 (2.37)	21.63 (3.69)	0.33*	0.72
Visit two	*n=80*	*n=22*			
Mean Age (sd)	22.82 (2.75)	23.17 (2.19)		0.54 [&]	0.59
Visit three	*n=29*	*n=4*			
Mean Age (sd)	24.46 (9.87)	24.85 (2.02)		0.07	0.79

Gender	**High Risk group n (%)**		**Control group n (%)**		**1st Episode group n (%)**		**Chi-square** χ^2	**p**
	Males	**Females**	**Males**	**Females**	**Males**	**Females**		
Visit one	79 (48.8)	83 (51.2)	17 (47.2)	19 (52.8)	25 (67.6)	12 (32.4)	4.57	0.10
Visit two	38 (47.5)	42 (52.5)	13 (59.1)	9 (40.9)			0.47	0.25
Visit three	12 (41.4)	17(58.6)	4 (100)				No statistics conducted as numbers too small	

Marital status At baseline	**High Risk, n=155 n (%)**	**Control, n=35 n (%)**	**Patients, n=37 n (%)**	**Chi-square** χ^2	**p**
Single	131 (84.5)	31 (88.6)	35 (94.6)	5.11	0.28
Married	20 (12.9)	2 (5.7)	2 (5.4)		
Separated	4 (2.6)	2 (5.7)	0 (0.0)		
At baseline No children	138 (89.0)	32 (91.4)	0 (0)		
One or more	17 (11.0)	3 (8.6)	0 (0)	0.17	0.68

*One-way analysis of variance. [&]Independent samples t-test

2.6.6. Learning difficulties (reading, writing, and speech problems)

Self reported learning difficulties, reading, writing, and speech problems, were assessed in the groups. For reading and/or writing problems, no learning difficulties and self reported difficulties were added together, and remedial classes and diagnosed dyslexia were added together. While all of the data were self reported it was felt that self reported difficulties that did not receive any educational intervention were often vaguely described by the subjects, and for this reason they were combined with no difficulties for the statistical analysis. Self reported speech problems were added together with none (given lack of any objective evidence) and compared to those who had speech therapy. A significant difference was found between the groups in terms of reading and writing difficulties. The main finding was that a significant excess of patients had had reading and /or writing problems during their childhood, which had required educational intervention. 26.3% of patients versus 7.8% of the HR group and 0% of the controls required specialist help for learning difficulties. None of the controls reported having any extra input for any learning difficulties in childhood. There was no significant difference between the groups in terms of the rate of speech difficulties during childhood.

Table 2.6.6. Learning difficulties (reading, writing, and speech problems)

	High Risk n (%) n=154	Controls n (%) n= 35	Patients n (%) n=33	Chi-square χ^2	p
Reading/writing problems					
No learning difficulties	128 (83.1)	32 (91.4)	24 (72.7)		
Remedial classes	8 (5.2)		5 (15.2)	10.14	0.006
Self reported difficulties but no intervention	14 (9.1)	3 (8.6)	2 (6.1)		
Diagnosed dyslexia	4 (2.6)		2 (6.1)		
Speech problems					
No speech problems	134 (87.0)	30 (85.7)	28 (84.8)	0.18	0.91
Self reported problems no speech therapy input	6 (3.9)	1 (2.9)	2 (6.1)		
Speech Therapy input	14 (9.1)	4 (11.5)	3 (9.1)		

2.6.7. Other school problems

Data were not available for all subjects. The number of cases for whom data were available is listed in the Table. None of the patients or controls had ever attended a residential school in comparison to 5 (3.2%) of the HR group. Time off school for truancy or for other reasons is outlined in Table 2.6.7. Statistical analysis was conducted on the truancy figures only. No truancy (self reported) was compared to mild and extreme truancy (self reported). A significant difference was found between the groups (χ^2 =5.96, p=0.05), and was accounted for by the patient group who had an ASR of +2 in the truancy positive cell. Amount of time off school for other reasons was low in all groups, only 3.7% in the HR, 8.6% in the control group, and did not occur in the patient group. The reasons were various, including time spent abroad and physical illness.

Table 2.6.7. Other school problems

	High Risk n (%) n=154	Controls n (%) n= 35	Patients n (%) n=33
Never in residential school	149 (96.8)	35 (100)	33 (100)
In residential school	5 (3.2)		
TIME OFF SCHOOL			
No time off school	124 (80.5)	30 (85.7)	24 (72.7)
Self reported mild truancy	5 (3.2)	2 (5.7)	
Self reported extreme truancy	19 (12.3)		9 (27.3)
Time off school for other reason (e.g. medical)	6 (3.7)	3 (8.6)	

2.6.8. History of psychological difficulties

The number of subjects for whom data were available regarding past psychological difficulties is presented in Table 2.6.8. The patients' past psychological history was not included in any statistical comparisons. It was unclear as to whether such difficulties were independent of the current illness or were indeed a manifestation of it, for this reason it was decided to only compare the high-risk and control groups. A chi-square analysis was conducted on the baseline information. Comparing those who had a reported psychological difficulty of any kind to those who did not, the high-risk group reported significantly (χ^2= 9.75, df 1, p=0.002) more problems (n=55/155 (35.5%) than the control group (n=3/35 (8.6%). The data presented for the second round of

assessments in Table 2.6.8 represents psychological difficulties reported at second round of assessments for the first time and similarly the data for the third round.

Table 2.6.8. History of psychological difficulties (information updated at each assessment)

ROUND ONE	High Risk n (%) n=154	Controls n (%) n= 35	Patients n (%) n=33
No reported difficulties	100 (64.5)	32 (91.4)	24 (72.7)
Saw GP/Counsellor for Depression	5 (3.2)	1 (2.9)	
Saw GP/Counsellor other psychological problem	18 (11.6)		4 (12.1)
YPU/psychiatric contact	15 (9.7)	1 (2.9)	3 (9.1)
Other problem	5 (9.7)		1 (3.0)
Attended Dept. of Child and Family Therapy	4 (2.6)	1 (2.9)	1 (3.0)
Depression/Anxiety requiring medication	8 (5.2)		
ROUND TWO *Difficulties emerging between time 1 and 2*	**High Risk n (%) n=76**	**Controls n (%) n= 21**	
No reported difficulties	62 (81.6)	20 (95.2)	
Saw GP/Counsellor other psychological problem	6 (7.9)		
YPU/psychiatric contact	2 (2.6)		
Other problem		1 (4.8)	
Depression/Anxiety requiring medication	6 (7.9)		
ROUND THREE *Difficulties emerging between time 2 and 3*	**High Risk n (%) n=23**	**Controls n (%) n= 4**	
No reported difficulties	18 (81.8)	4 (100)	
Saw GP/Counsellor other psychological problem	1 (4.5)		
Depression/Anxiety requiring medication	4 (13.6)		

2.6.9. Forensic history

Information relating to forensic history is presented in Table 2.6.9. The information was updated at each assessment, thus information presented for round two and round three represent new forensic incidents. It was difficult to determine in a clear manner whether the involvement reported by the first episode patients was characteristic of the illness itself or if it was a precursor. For this reason it was decided that only the high-risk and controls would be statistically compared as the information was prospectively collected in these groups. Forensic history was defined as none, or forensic history other categories combined for the purpose of statistical analysis.

Chi-square analysis revealed no significant difference between the high-risk and control groups in terms of forensic history (χ^2= 2.30, df 1, p=0.13).

Table 2.6.9.Forensic history (information updated at each assessment)

ROUND ONE	High Risk n (%) n=155	Controls n (%) n= 35	Patients n (%) n=33
No forensic history	114 (73.5)	30 (85.7)	21 (63.6)
Police involvement, no charges/convictions	21 (13.5)	4 (11.4)	5 (15.2)
Police involvement, charges/convictions	17 (11.0)	1 (2.9)	7 (21.2)
Self reported (not caught)	1 (0.6)		
Imprisonment	2 (1.3)		
ROUND TWO *Difficulties emerging between time 1 and 2*	**High Risk n (%) n=78**	**Controls n (%) n= 21**	
No forensic history	75 (96.2)	20 (95.2)	
Police involvement, no charges/convictions	2 (2.6)	1 (4.8)	
Police involvement, charges/convictions	1 (1.3)		
ROUND THREE *Difficulties emerging between time 2 and 3*	**High Risk n (%) n=24**	**Controls n (%) n= 3**	
No forensic history	24 (100)	3 (100)	

2.6.10 Social work involvement and appearance before the children's panel

The rate of past social work involvement in the groups is presented in Table 2.6.10. The statistical analysis was conducted to compare the high-risk and control groups only. The patient group data is presented for comparison. Compared to controls, a chi square analysis revealed that the high-risk group had significantly more social work involvement (χ^2= 7.75, df 1, p=0.005) in their lives than the controls. Social work involvement was dichotomised as none or some. Appearance before the children's panel was exclusive to the high-risk group occurring in 14.9% of cases compared to none of the controls. The reasons for appearance before the children's panel are outlined in Table 2.6.10. 5.9% of the HR group had been fostered and 3% of the patients, but none of the controls. Also 3.9% of the HR group and 3% of the patients had been in care at some time, but none of the controls.

Table 2.6.10. Social work involvement and appearance before the children's panel

	High Risk n (%) n=154	Controls n (%) n= 35	Patients n (%) n=33
SOCIAL WORK INPUT			
None	111 (72.1)	33 (94.3)	31 (94.0)
Fostered	9 (5.8)		1 (3.0)
Other family involvement	25 (16.2)	2 (5.7)	
In Care	6 (3.9)		1 (3.0)
Social work input due to childrens panel attendence	3 (2.0)		
	High Risk n (%) n=154	**Controls n (%) n= 35**	**Patients n (%) n=33**
APPEARANCE BEFORE CHILDRENS PANEL			
No	131 (85.1)	35 (100)	21 (97.0)
Due to truancy	5 (3.2)		1 (3.0)
Due to other behavioural problems	8 (5.2)		
Due to family problems	6 (3.9)		
Other	4 (2.6)		

2.6.11. Alcohol consumption

Information about the past and current history of alcohol usage was collected in the groups and is presented in Table 2.6.11. Subjects reported their alcohol consumption as units of alcohol per week. This information was re-categorised according to the recommended guidelines of safe alcohol consumption, 14 units per week for women and 21 units for men. This categorical variable was then used for statistical analysis. Only information for the controls and the HR group is presented as the data were thought to be unreliable in the patient group, again for the reason that the alcohol consumption might be related to the illness. A chi-square test was conducted and no significant difference was found between the groups in terms of rate of alcohol consumption past or present (χ^2= 1.51, df 2, p=0.47) as reported at baseline assessment, at second round assessment (χ^2= 2.37, df 2, p=0.31) or at third round of assessment (χ^2= 1.56, df 2, p=0.46). Past and present alcohol consumption estimates were identical.

Table 2.6.11. Alcohol consumption

ROUND ONE	High Risk n (%) n=154	Controls n (%) n= 35
ALCOHOL USAGE		
None	**25 (16.4)**	**3 (8.3)**
Within the maximum recommended limit	**93 (61.2)**	**24 (66.7)**
More than the maximum recommended limit	**34 (22.4)**	**9 (25.0)**
ROUND TWO	**High Risk n (%) n=76**	**Controls n (%) n= 18**
ALCOHOL USAGE		
None	10 (13.2)	3 (16.7)
Within the maximum recommended limit	50 (65.8)	14 (77.8)
More than the maximum recommended limit	16 (21.1)	1 (5.6)
ROUND THREE	**High Risk n (%) n=20**	**Controls n (%) n= 4**
ALCOHOL USAGE		
None	3 (15.0)	
Within the maximum recommended limit	15 (75.0)	2 (66.7)
More than the maximum recommended limit	2 (10.0)	1 (33.3)

2.6.12. Current and past drug usage; cannabis

Cannabis usage was categorised as none, occasional, and frequent/severe usage. The information for the high-risk and controls is presented in Table 2.6.12. There was no significant difference between the groups in terms of current cannabis usage for round one (χ^2= 2.01, df 2, p=0.37) or round two (χ^2= 5.59, df 2, p=0.06). Similarly there were no differences for past usage at round one (χ^2= 3.43, df 2, p=0.18) or round two (χ^2= 5.11, df 2, p=0.08). The rate of other drug usage in the groups was measured and no differences were found between the groups for current usage at round one (χ^2= 0.50, df 2, p=0.78) or past usage at round one (χ^2= 0.10, df 2, p=0.95). Similarly no group differences were identified for current other drug usage at round two (χ^2= 0.53, df 2, p=0.77) or past usage at round two (χ^2= 0.87, df 2, p=0.65).

Table 2.6.12. Current and past drug usage; cannabis

ROUND ONE	High Risk n (%)		Controls n (%)	
	Current n=153	Past n=152	Current n=36	Past n=36
CANNABIS USAGE				
None	105(68.6)	66 (43.4)	29 (80.6)	15 (41.7)
Occasional	34 (22.2)	67 (44.1)	5 (13.9)	20 (55.6)
Frequent/Severe	2 (9.2)	19 (12.5)	2 (5.6)	1 (2.8)
ROUND TWO	**High Risk n (%) n=76**		**Controls n (%) n=18**	
	Current	Past	Current	Past
CANNABIS USAGE				
None	52 (68.4)	29 (38.2)	17 (94.4)	12 (66.7)
Occasional	19 (25.0)	39 (51.3)	1 (5.6)	6 (33.3)
Frequent/Severe	5 (6.6)	8 (10.5)		
ROUND THREE	**High Risk n (%) n=21**		**Controls n (%) n= 3**	
	Current	Past	Current	Past
CANNABIS USAGE				
None	15 (71.4)	9 (42.9)	3 (100)	3 (100)
Occasional	5 (23.8)	11 (52.4)		
Frequent/Severe	1 (4.8)	1 (4.8)		

2.6.13 Present State Examination ratings at each assessment

The PSE (Wing et. al., 1974) was used as the principal method of psychopathological assessment. A substantial number of high-risk participants had relatively little in the way of symptomatology because this study was done on a population, which, at entry, saw itself as well. To take account of this and to simplify consideration of the psychopathology as determined by the PSE, a simplified classification was drawn up on the basis of the PSE profiles (Johnstone et al., 2000). The essence of the study PSE classification is as follows:

4 -Schizophrenia

3 -Specific psychotic features fully rated

2 -Specific psychotic features partially rated and some other possibly psychotic symptoms (e.g. perceptual distortions) fully rated.

1 -None of the above features but another symptom or behavioural items fully rated.

0 -None of the above

The scores of 3 generally represent fully held auditory or visual hallucinations but occasionally an isolated delusion. In order to examine neuropsychological associations with mental state the HR group were split according to absence or presence of psychotic symptoms. Those with no psychotic symptoms (study PSE scores of 0 or 1) at any of the assessments were compared with those who had psychotic symptoms in partial or definite degree (study PSE scores 2 or 3) at either assessment.

Subjects were rated according to the 9th edition of the Present State Examination and the data is presented in Table 2.6.13. Differences between the HR and control groups were investigated. Mann Whitney U tests were performed on the data and revealed that at baseline assessment ($Z=-2.28$, $p=0.02$), and round two assessments ($Z=-2.41$, $p=0.02$) the high-risk group scored significantly higher on the PSE than the controls. This was not the case at round three where no significant differences were found between the groups ($Z=-0.45$, $p=0.75$). It should be noted that no persons received a PSE 4 at round 1 and those who did become psychotic between assessments were not included in the follow up statistics presented above. The numbers were however, very small at round three. PSE symptoms were further categorised as ever having symptoms (data were combined across assessments with subjects categorised according to the highest symptom they ever scored) and the data is presented in Table 2.6.14. A Mann Whitney U test was performed on the data revealing that high-risk subjects scored significantly higher on the PSE overall, compared to the controls ($Z=-2.34$, $p=0.019$).

Table 2.6.13.1. Present State Examination ratings at each assessment

ROUND ONE	High Risk n (%) n=152	Controls n (%) n= 36
PSE SYMPTOMS		
None	82 (53.9)	27 (75.0)
SCORE OF 1	31 (20.4)	5 (13.9)
SCORE OF 2	17 (11.2)	1 (2.8)
SCORE OF 3	22 (14.3)	3 (8.3)
ROUND TWO	**High Risk n (%) n=78**	**Controls n (%) n= 19**
PSE SYMPTOMS		
None	51 (65.4)	18 (94.7)
SCORE OF 1	19 (24.4)	1 (5.3)
SCORE OF 2	3 (3.8)	
SCORE OF 3	4 (5.1)	
SCORE OF 4	1 (1.3)	
ROUND THREE	**High Risk n (%) n=23**	**Controls n (%) n=4**
PSE SYMPTOMS		
None	16 (69.6)	3 (75.0)
SCORE OF 1	1 (4.3)	1 (25.0)
SCORE OF 2	2 (8.7)	
SCORE OF 3	3 (13.0)	
SCORE OF 4	1 (4.3)	

Table 2.6.13.2. PSE Symptoms ever

ROUND ONE	High Risk (valid %) n=152 (10 missing)	Controls (valid %) n= 36
HIGHEST EVER SCORE OBTAINED ON PSE		
NO SCORE	74 (47.7)	26 (72.2)
SCORE OF 1	34 (21.9)	6 (16.7)
SCORE OF 2	19 (12.3)	1 (2.8)
SCORE OF 3	18 (11.6)	3 (8.3)
SCORE OF 4	10 (6.5)	

2.6.14. Comparison of those who returned for the second round of assessments among the control and high-risk group and those who did not

In a descriptive manner both groups were divided into those who returned for a second round of assessment and those who did not, in an attempt to identify possible risks factors for attrition in the groups. The results are presented in Appendix 1 in Tables 2.6.14.1 to 2.6.14.10. From the Tables it can be seen that there were no strikingly obvious variables that differentiated those who returned from those who did not.

CHAPTER THREE: METHODOLOGY OF THE NEUROPSYCHOLOGICAL ASSESSMENTS

3.1. Neuropsychological Assessment Battery

The test battery chosen was designed to include tests which have been previously shown to differentiate subjects at high-risk for schizophrenia and controls (Kremen et al., 1994). Tests showing differences between schizophrenia patients and controls, and tests that localise to parts of the brain which have been shown on imaging or other investigations to differ between schizophrenia patients and controls, were also chosen. The battery was designed to be repeatable and not so prolonged that compliance would be reduced. The neuropsychological assessments were organised according to neuropsychological functions on the basis of general neuropsychological practice (Lezak, 1995), and in a manner similar to previous studies of adult relatives of patients with schizophrenia (Kremen et al., 1992, 1994). The tests administered, at each assessment, and the functions they serve to examine are outlined in Tables 3.1 to 3.3. The battery was extensive and covered many domains of function. The reason for this wide-ranging cognitive assessment was to try to identify any differences between the subjects in any area of cognitive function. It was felt that it would be best to try to cover a broad range of functioning given the possible areas of dysfunction identified by previous research with high-risk populations and populations of persons with a schizophrenic illness.

Table 3.1. Neuropsychological Assessment battery: baseline (3 ½ hours)

NEUROPSYCHOLOGICAL FUNCTION	TESTS
Current intellectual function	Wechsler Adult Intelligence Scale Revised (WAIS-R; Wechsler, 1981)
	Speed and Capacity of Language Processing test (Baddeley et al., 1992)
Premorbid intellectual Function	National Adult Reading Test (Nelson and O'Connell, 1978; Nelson, 1982)
	The Schonell Graded Word Reading Test (used in conjunction with the NART)
Executive function	Hayling Sentence Completion Test (Burgess and Shallice, 1996)
	Stroop Colour Word Test (computerised translation of Golden, 1978)
	Verbal Fluency (FAS) and Semantic category, animals (Spreen and Strauss, 1991)
Perceptual motor speed.	WAIS-R Digit-symbol age scaled scores (Wechsler, 1981)
Mental control/encoding	WAIS-R Digit span (Wechsler, 1981) forwards and backwards
	WAIS-R Arithmetic age scaled scores (Wechsler, 1981)
Sustained attention	Continuous Performance Test-Identical Pairs Version (CPT-IP, version A; Cornblatt et al., 1988)
Verbal ability and language	Token test (Spreen and Benton, 1969,1977)
	WAIS-R Vocabulary age scaled scores (Wechsler, 1981)
Learning and memory	
Procedural memory	Rivermead Behavioural Memory Test (Version A (red); Wilson et al., 1985).
Verbal learning	Rey Auditory Verbal Learning Test (Rey, 1964).
Visual memory	Wechsler Memory Scale -Revised, Visual Reproductions, immediate and delayed conditions (Wechsler, 1987).
Handedness	Hand preference (Annett, 1970; Oldfield, 1971)

Table 3.2. Neuropsychological Assessment battery: round two (2¼ hours).

NEUROPSYCHOLOGICAL FUNCTION	TESTS
Current cognitive function	WAIS-R Block Design test (Wechsler, 1981)
	Speed and Capacity of Language Processing (Baddeley et al., 1992)
Executive function	Hayling Sentence Completion Test (Burgess and Shallice, 1996)
	Stroop Colour Word Test (computerised translation of Golden, 1978)
	Verbal Fluency (FAS) and Semantic category, animals (Spreen and Strauss, 1991)
	Trails A and B
Perceptual motor speed.	WAIS-R Digit-symbol age scaled scores (Wechsler, 1981)
Mental control/encoding	WAIS-R Digit span (Wechsler, 1981) forwards and backwards
Sustained attention	Continuous Performance Test-Identical Pairs Version (CPT-IP, version B; Cornblatt et al., 1988)
Verbal ability and language	Token test (Spreen and Benton, 1969,1977)
Learning and memory Procedural memory	Rivermead Behavioural Memory Test (Version B (blue); Wilson et al., 1985).
Verbal learning	Crawford version of the Auditory Verbal Learning Test (Crawford et al., 1989).
Visual memory	Wechsler Memory Scale —Revised, Visual Reproductions, immediate and delayed conditions (Wechsler, 1987).
Handedness	Hand preference (Annett, 1970; Oldfield, 1971)

Table 3.3. Neuropsychological Assessment battery: round three (1 hour).

NEUROPSYCHOLOGICAL FUNCTION	TESTS
Current cognitive function	WAIS-R Block Design test (Wechsler, 1981)
	Speed and Capacity of Language Processing (Baddeley et al., 1992), Speed of comprehension Test
Executive function	Hayling Sentence Completion Test (Burgess and Shallice, 1996)
	Stroop Colour Word Test (computerised translation of Golden, 1978)
	Verbal Fluency (FAS) and Semantic category, animals (Spreen and Strauss, 1991)
	Trails A and B
Perceptual motor speed.	WAIS-R Digit-symbol age scaled scores (Wechsler, 1981)
Mental control/encoding	WAIS-R Digit span (Wechsler, 1981) forwards and backwards
Learning and memory	
Procedural memory	Rivermead Behavioural Memory Test (Version C (green); Wilson et al., 1985).
Verbal learning	Jones-Gotman et al. version of the Auditory Verbal Learning Test (Jones Gotman, Sziklas, and Majdan, reported by Lezak, 1995, page 441)

3.2. Current and Premorbid Cognitive Functioning

Current cognitive function was assessed by means of the Wechsler Adult Intelligence Scale- Revised (WAIS-R; Wechsler, 1981) and the Speed and Capacity of Language Processing test (SCOLP; Baddeley et al., 1992).

3.2.1. The Wechsler Adult Intelligence Scale-Revised

The WAIS-R (Wechsler, 1981) is the revised edition of the 1955 Wechsler Adult Intelligence Scale. The WAIS-R is a measure of general intelligence. It was standardised on a sample of 1880 adult American subjects between 1976 and 1980. The WAIS-R was used in this study to assess the current level at which the individual was functioning when they enter the study. The WAIS-R is composed of

eleven different subtests, six verbal and five performance (non-verbal) tests. The test yields a Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ). The verbal subtests include; Information (General knowledge questions); Digit Span (recall of sequences of numbers forwards and in reverse); Vocabulary; Arithmetic; Comprehension (questions reflecting degree of socialisation and social awareness and common sense); Similarities (subjects requested to suggest a manner in which two items are alike). The performance scale includes; Picture Completion (identify something missing from each of a series of pictures); Picture Arrangement (arrange pictures in correct order to tell a story); Block Design (create designs from pictures using blocks); Object Assembly (correctly arrange pieces to make up a complete object); Digit Symbol (fill in the corresponding symbols from a template of numbers and symbols into the blank boxes beneath rows of numbers). While the WAIS-R was standardised on an American sample, the version of the test used in this study is one modified for use on British samples. British norms have been provided by Crawford et al., (1995). The modifications undertaken are well described by Lea (1986). Items were replaced if they were judged to be so culture specific that they could have a markedly different difficulty level for British subjects. Substitute items were chosen to have a similar content to the original items they replaced. Wherever possible the original items were modified rather than replaced. The raw scores are converted to scaled scores, which account for age. The scaled scores used in the British version are those derived from the American sample. The digit symbol, digit span, arithmetic, and vocabulary subtests were individually separated out of the overall test results as specific measures of perceptual motor speed (digit symbol), mental control /encoding (digit span, arithmetic), and verbal ability and language (vocabulary). The block design subtest was presented at the 2nd and 3rd assessment point, as a measure of general mental ability. This is the most commonly used intelligence test and has good reliability and validity (Wechsler, 1981). Factor analytic studies suggest that the WAIS-R is composed of one, two, or three factors with most studies reporting a 3-factor model (O'Grady, 1983; Plake et al., 1987; Waller and Waldman, 1990; Burton et al., 1994; Burgess et al., 1992). The three factor models specify verbal comprehension (VC), perceptual organisation (PO), and freedom from distractibility (FFD). The FFD factor is composed of digit span, digit

symbol, and arithmetic, those tests requiring attention and concentration abilities. There is some contention about the justifiability of the three-factor model, with Enns and Reddon, (1998) suggesting a one or two factor model to be more appropriate.

3.2.1.1. Data generated: WAIS-R

Full scale IQ, Verbal IQ, and Performance IQ were generated. Also differences between Performance and Verbal IQ were generated. Also the individual subtests, digit symbol, digit span forwards and backwards, arithmetic, and vocabulary were examined individually.

Administered independently at second and third round assessment

3.2.2. Block Design

This subtest of the WAIS-R (Wechsler, 1981) involves the spatial component in perception, at the conceptual level, and a motor execution (Lezak, 1995). The subject is presented with 9 blocks, each are made up of two sides that are red, two sides that are white, and two sides that are mixed in colour, half red and half white, and are split along the diagonal. The requirement is to use the bocks to construct replicas of 2 block constructions made by the examiner and seven designs printed on a page. Five of the designs have a one-minute time limit and involve 4 blocks; the remaining four have nine blocks and a time limit of 2 minutes. Extra points can be gained from design 3 to 9 for speedy performances. Education effects tend to be low for the 16-19 year old age group (Kaufman et al., 1988) but account for 15% to 24% of the variance in the 35-74 year age range. Factor analytic studies demonstrate high loadings for block design on the perceptual organisation factor regardless of the number of factors derived or age (Parker, 1983). In addition to measuring visuospatial organisation (Lezak, 1995) this test correlates highly with general mental ability (Benton, 1984), and cognitively capable but academically or culturally limited persons frequently obtain their highest scores on this test. In normal subjects block design performance was associated with increased metabolism in the "posteroparietal region" particularly of the right side as seen by PET scans (Chase et al., 1984). It is recognised as a good measure of brain damage, particularly to the parietal regions (McFie, 1975).

3.2.2.1. Data generated for analysis: Block design

This test was administered independently of the WAIS-R on the second and third round of assessments. Age adjusted scale scores were calculated and compared to previous performances on this task, i.e. scores at time 1-scores at time 2, to search for either decrements or improvements over time.

3.2.3. The Speed And Capacity Of Language Processing Test

The Speed and Capacity of Language Processing test (Baddeley et al, 1992) was designed to measure slowing in cognitive processes resulting from brain damage. There are two sections of the SCOLP, the Speed of Comprehension test, which measures the rate of information processing and the Spot the Word test, which provides the framework for interpreting the results of the first test. The test can enable the differentiation between a subject who has always been slow and a subject whose performance has been impaired as a result of brain damage or some other stressor. The SCOLP is described as holistic rather than analytic (i.e. measuring a specific function). It was designed to provide a holistic measure of the efficiency of language comprehension. The speed with which subjects can verify statements about the world is correlated with VIQ. Poor performance may mean the subject is low in verbal skills or it may represent the effect of brain damage. Spot the Word test provides a relatively crystallised and robust estimate of VIQ and is believed to be less likely to be influenced by brain damage. The extent to which a subjects Speed of Comprehension falls below that anticipated by their Spot the Word performance will give an indication of the extent to which their language comprehension skills have been depressed.

The Spot the Word test is described as a supplement to the NART. Instead of requiring the individual to read aloud, it requires them to make a silent lexical decision. The Spot the Word test avoids some of the problems associated with the NART. It does not require the capacity to read aloud; it requires familiarity but not necessarily the capacity to pronounce correctly (thus not penalising those who gain vocabulary from reading), it is adaptable to any language. It can be given as a group

test; it is a silent test on which failure causes little embarrassment. The Speed of Comprehension correlates with VIQ so poor performance on the Speed of Comprehension test may reflect either an intrinsically low level of verbal competence or a decrement from a previously high level of ability. To decide between these two possibilities, it is necessary to have an independent estimate of verbal capacity. It is also thought to be relatively resistant to acquired organic impairment. The Spot the Word test can be used for this purpose. The test was developed as an estimator of pre-morbid IQ. Performance on the test was found to correlate highly with VIQ as measured by the Mill Hill Vocabulary test (Raven et al., 1982) and performance on the NART (Baddeley et al., 1992). Performance on this test was found not to decline with age (Baddeley et al., 1993). The Speed of Comprehension test can also be used as a measure of semantic memory (McKenna et al., 1995, page 280).

The ***Speed of Comprehension test*** consists of a series of sentences about the world, half of which are true and half are false. The false sentences are created by mismatching the predicate and the subject from two correct statements. The subject is given 2 minutes to identify whether each of the 100 sentences is true or false. Examples of sentences are *"Nuns are made in factories" "Pythons move around searching for food"*. Before the subject begins the main test they complete a practice session of 6 sentences. Performance is measured in terms of the number correctly categorised in 2 minutes.

The ***Spot the Word test*** consists of pairs of words, one real and one nonsense word invented to look like a real word but having no meaning. The subject must identify and place a tick beside the real word in each of the 60 pairs of items. There is no time limit on the test. Examples include; "bread — glot" and "kitchen - harrick". Before the subject begins the main test they complete a practice session of 6 pairs of items to ensure no unforeseen problems arise. Subjects are encouraged to guess if they are not sure and in this study, subjects were encouraged to indicate where they were guessing by placing a "?" beside the ticked item.

3.2.3.1. Data generated: Speed And Capacity Of Language Processing Test

Total number of correctly identified sentences. Total number of correctly identified words on the paired words task. All converted to scaled scores. The number of errors on the Speed of Comprehension test was also recorded.

3.2.4. The National Adult Reading Test (NART)

The NART (Re-standardised version, Nelson, 1982) was employed to measure the individuals premorbid FSIQ, and is simply refered to as NART in the text. The test consists of a list of 50 words, which the person is requested to read. The number of errors on this test is used to estimate premorbid Intelligence. The NART was designed to provide a means of estimating the premorbid IQ levels of adult patients suspected of suffering from intellectual deterioration. Reading ability is known to highly correlate with general IQ level in the normal population (Nelson and McKenna, 1975). The words chosen for the NART are words which have atypical grapheme-phoneme conversions e.g. drachm, gauche, naive. Therefore individuals must have prior knowledge of how the word is pronounced to be able to read it accurately. The 50 words are organised in order of increasing difficulty, and they are short. WAIS-R VIQ, PIQ, and FSIQ can be predicted from the reading error score by inserting it into the appropriate formula (Nelson, 1982). Conclusions may be drawn about the probable extent of intellectual decline based on the discrepancy between the premorbid IQ predicted from the NART score and the actual IQ obtained by the WAIS-R. A positive predicted minus obtained IQ discrepancy suggests that previously the subject may have functioned at a higher intellectual level than the present one, and the larger the positive discrepancy the more likely it is that to represent intellectual decline. A negative predicted minus obtained discrepancy has no specific clinical implications and in the normal population is of little or no significance. It may be due to a lack of opportunity to develop reading skills, e.g. the result of poor schooling, or English may not be the first language. The NART was reported to be a reliable test (O'Carroll, 1987; Crawford et. al., 1988) even when used by clinically naive raters. The validity of the NART as a measure of general IQ in the normal adult population has been confirmed (Crawford et al., 1988). If the predicted FSIQ (NART) minus the observed FSIQ (WAIS-R) was 15

or greater, cognitive decline is suspected. It was found to be a reasonable estimate of pre-morbid ability in acutely ill, unmedicated schizophrenic patients (O'Carroll et al., 1992).

3.2.4.1. Data generated: NART

NART FSIQ was generated.

3.2.5. The Schonell Graded Word Reading Test

If fewer than 10 NART words are read correctly then the accuracy of the IQ predictions is increased if the NART results are combined with the results of the Schonell Graded Word Reading Test (SGWRT). The Schonell contains many easier words so that whereas the NART can only be used reliably to predict IQ in the average range and above, the addition of the Schonell words extends the range of prediction down to the borderline/defective range (Nelson, 1982). The NART error score and the Schonell error score can be combined and a WAIS-R FSIQ can be predicted. The Schonell reading test is given to each of the participants. The Schonell consists of a list of 100 words beginning at a basic level. In addition to the combined predictive ability of the Schonell and the NART in some individuals the Schonell is also used in this study to assess subjects reading ability in preparation for the more difficult NART and to instil some confidence in the individuals reading ability prior to the administration of the more difficult NART. If an individual shows signs of difficulty reading the basic words on the Schonell then some form of specific reading difficulty is suspected.

3.2.5.1. Data generated: Schonell Graded Word Reading Test

Total number of correctly read words.

3.3. Executive Function

3.3.1. Hayling Sentence Completion Test

The Hayling Sentence Completion Test (HSCT, Burgess and Shallice, 1996) is a relatively new test. It is a test of response suppression. It is comprised of two conditions, in both the sentence must be completed as quickly as possible, with a

one-word answer. In the first condition (response initiation), subjects are required to finish a sentence by inserting a word that sensibly completes the sentence. In the second condition (response suppression) subjects are required to give a ridiculous ending to the sentence by inserting a word that makes no sense in the context of the sentence (incongruous condition). The errors are scored according to the degree of sense made by the sentence completion. Category A errors are scored if a sentence in the incongruous condition is correctly completed. Category B errors are scored if the sentence makes some sense *e.g. The whole town came to hear the Mayor_____, answer: Sing.* Raw scores are then converted to scaled scores. Good performance on this test requires active cognitive inhibition.

3.3.1.1. Data generated: Hayling Sentence Completion Test

Time in seconds taken to complete section A. Converted scaled scores of category A and category B errors, also total errors. Time on section B minus time on section A, to remove the speed element.

3.3.2. Stroop Colour Word Test

The version of the Stroop used here, was a computerised version of that by Golden, (1978), a straightforward translation of the 'paper and pencil test'. The computerised version was kindly supplied to us by Dr Richard Brown, at the MRC Human Movement and Balance Unit, Institute of Neurology, Queens Square, London. There were three conditions, firstly a baseline condition where colour words were presented in white against a black background, arranged in four rows of five words. The colour words were red, green, blue, and yellow. The subject was instructed to read each row from left to right until they reached the end, they were encouraged to read as quickly as possible and correct any mistakes they made. They were notified to begin only after they heard a bleep, which heralded the beginning of the timer. The second condition consisted of four rows of rectangular blocks of the colours, red, green, blue, and yellow. The instructions to the subject were the same. In the final test condition, the incongruous condition, four rows of five colour words (red, green, blue, yellow) were presented again, however, this time, the words were written in incongruous ink. The same instructions were given to the subject. The Stroop task

has received many interpretations; some workers have attributed the slowing in the incongruous condition to a response conflict, some to failure of response inhibition, and others to a failure of selective attention (Dyer, 1973, Zajano and Gorman, 1986). Lezak's (1995) clinical interpretation is that patients who fail it tend to have difficulty concentrating, and get easily distracted. The activity required by the test was said to be that of the selective processing of "only one visual feature while continuously blocking out the processing of others" (Shum et al., 1990). It seems to be a measure of concentration effectiveness (Lezak, 1995). The reliability of this test is satisfactory according to Spreen and Strauss (1991). Practice effects have been reported for the colour-word interference trial for the second administration but not subsequent ones (Connor et al., 1988). Both age and intellectual level may contribute to performance on the Stroop test (Das 1970). Perret (1974) related performance on the Stroop to left frontal lobe damaged patients and not to other patients or control groups.

3.3.2.1. Data generated: Stroop Colour Word Test

Time in seconds as measured by the computer and error scores as measured by the examiner, were recorded. There were few errors made on this task, and it is known that young adults rarely make errors (Lezak, 1995).

3.3.3. Verbal Fluency

This test is also known as the Controlled Oral Word Association test, FAS test or Word Fluency (Spreen and Strauss, 1991). The purpose of this test is the spontaneous production of words beginning with a letter or of a given class within a limited amount of time (verbal association fluency). The subject is asked to produce as many words as possible that begin with a given letter, typically for 1 minute. The letters in this case were FAS. The most commonly used letters for this test. Also the subjects were requested to recall the names of as many four legged animals as they could. A stopwatch was used to keep account of the time. One minute was given for each letter and animal category. Inadmissible words produced were not counted as correct, however there was no negative scoring. Inter-scorer reliability is reported to be near perfect; one-year retest reliability in older adults has been reported as .70 for

F, 0.6 for A and 0.71 for S, Snow et al., (1988). Impaired verbal fluency has also been associated with frontal lobe damage (e.g. Perret 1974). Pet studies suggested that both frontal and temporal regions participate bilaterally in the system (Parks et al., 1988). Performance is known to be influenced by age, gender, and education (Benton et al., 1983).

3.3.3.1. Data generated: Verbal Fluency

The test was scored by summing all of the admissible words for the 3 letters, 'FAS'. Also the total number of valid animal names produced was counted.

3.3.4. Trails Making Test A & B

This test is widely accepted to be a test of visual conceptual and visuomotor tracking. It is in the public domain, having been originally part of the Army Individual Test Battery (1944). There are two sections, A and B. In section A the subject must connect a series of numbers from one to 25 without taking the pen/pencil from the page. The numbers are encircled and dispersed around the page. In the second condition encircled numbers again appear, however this time each number has a corresponding letter of the alphabet (also encircled). The purpose is to join the number to the corresponding letter and then proceed to the next number followed by its corresponding letter, and so on. The subject has to complete the task as quickly as possible without taking the pen from the page. The task is difficult and errors may often occur. The examiner must tell the subject when an error has been made allowing the subject to make a correction. This is the most common format of the test (Lezak, 1995). This test therefore depends upon the speed at which the examiner notes and informs the subject of the errors and also the speed at which the subject comprehends the instructions and makes the changes. It is also a test of complex visual scanning with a motor component (Shum et al., 1990), with motor speed and agility making a strong contribution to success on the task (Schear and Sato, 1989). Large differences between B and A suggest difficulties with conceptual tracking. Slow performances at any age on one or both parts A and B point to possible brain damage, but not which type of problem it may predominantly be (Lezak, 1995).

There is support linking this test to frontal activation (Segalowitz et al., 1992). Spreen and Strauss (1991) refer to this test as a "test of speed for visual search, attention, mental flexibility, and motor function". Lezak (1995) reported a high reliability of 0.98 for part A of this test and 0.67 for part B (using the coefficient of concordance). However, for patients with schizophrenia the reliability was 0.36 for part A and 0.63 for part B (Goldstein and Watson, 1989).

3.3.4.1. Data generated: Trails Making Test A & B

Time taken to complete each section, with errors corrected. Also a difference score of time on B minus time on A essentially removes the speed element (Lezak, 1995).

3.4. Perceptual motor speed

3.4.1. Digit Symbol

The digit symbol subtest of the WAIS-R was analysed independently of WAIS-R FSIQ, it was intended as a measure of perceptual motor speed. The test consists of four rows of 100 small blank squares, each paired with a randomly assigned number from one to nine. Above the test there is a key that pairs each number with a nonsense symbol. The objective is to consecutively fill in the blank spaces, working as quickly as possible, for 90 seconds. Copying speed was found to be important for this test (Storandt's, 1976) accounting for 72% of the variance (Le Fever's, 1985). It is also affected by visual perception and visual orientation ability (Lezak, 1995). For most adults it is a test of psychomotor performance, and it has been said that it tends to be unaffected by intelligence, memory, or learning. (Erber et al, 1981; Glosser, et al., 1977; Murstein and Leipold, 1961). Also motor persistence, sustained attention, response speed and visuomotor co-ordination play important roles in a normal person's performance (Lezak, 1995). A perceptual organisation component and a selective attention factor and incidental memory component have been reported for this test (Lezak, 1995). Practice effects may occur (Youngjohn et al., 1992). High test-retest reliability has been found for this test with correlations in the range of 0.82 to 0.88 (Wechsler, 1981; Matarazzo and Herman, 1984; Youngjohn et al., 1992). Performance by schizophrenic patients was not stable with test retest reliabilities of 0.38 (Goldstein and Watson, 1989). Mental ability does not seem to contribute

greatly to this test (Wechsler, 1981). This test is very sensitive to brain damage; its score is most likely to be depressed even when damage is minimal (Lezak, 1995). In factor analytic study of the WAIS-R this test loads greatest on a factor called memory/freedom from distractibility (Kaufman, 1979).

3.4.1.1. Data generated: Digit Symbol

The score is the number of squares filled in correctly within the time limit, converted to the WAIS-R age corrected scaled score.

3.5. Mental control/encoding

3.5.1. Digit Span

This is a subtest of the WAIS-R. The test has two components, digits forwards, and digits backwards, each involving different mental activities and are affected differently by brain damage. It is therefore important to separate out these two sections and assess performance on each one individually. The digit span subtest was used here as a measure of mental control/ encoding. The test consists of seven pairs of random number sequences, which were read out to the subject at the rate of one per second. The subject was then required to recall the sequence in the same order. Both digits forward and digits backwards involve auditory attention and depend on a short-term retention capacity (Shum et al., 1990).

3.5.1.1. Digits Forwards:

Lezak (1995) recommends recording the raw scores. It consists of pairs of sequences of numbers from 3 to 9 digits, which subjects are read aloud at a rate of one per second and are required to recall the numbers in the given sequence. The normal range is a sequence of 6 ± 1. Education appears to have a strong effect on this task. Digits forwards load most highly on the freedom from distractibility factor (Kaufman, 1979) being more closely related to the efficiency of attention than to memory. Practice effects were found to be significant but negligible with test re-test reliability coefficients ranging from 0.66 to 0.89 (Lezak, 1995).

3.5.1.2. Digits Backwards:

Digits reversed is a test of mental tracking. It tests how many bits of information a person can attend to at once and repeat in reverse order. It involves some perceptual tracking or more complex mental operations, many involving some form of visual scanning (Lezak, 1995). It consists of pairs of sequences of numbers from 2 to 8 digits which subjects are read aloud at a rate of one per second. They are required to recall them in the reverse order. The numbers must be stored briefly while reversing them mentally. This calls upon the working memory as distinctive from digits forwards and is therefore more of a memory test (Lezak, 1995). It involves mental double tacking as the memory of the numbers and reversing them must happen at the same time.

3.5.1.3. Data generated for analysis: Digits forwards and Digits backwards

Total raw score for digits forwards and digits backwards. Also scores according to cut-offs suggested by Lezak (1995) were examined. A score of 5 was considered marginal to normal, a score of 4, borderline, and a score of 3 was considered to be defective for digits forwards. For digits backwards a raw score of 4 or 5 could be considered normal, a score of 3 as borderline defective or defective, and a score of 2 as definitely defective.

3.5.2. Arithmetic

This is a WAIS-R subtest. The test consists of 14 items, but testing normally begins at the 3rd item since the first two are ordinarily given only to people who fail both items 3 and 4. Items have time limits ranging from 15 to 120 seconds. Raw score bonus points can be achieved for particularly rapid responses on the last 4 items. Difficulties in immediate memory, concentration or conceptual manipulation and tracking can prevent even very mathematically skilled patients from doing well on this orally administered test (Lezak, 1995). Educational effects were found to be prominent (Finlayson et. al., 1977). From age 20 men out perform women to a significant degree (Lezak, 1995). Split half reliability measures have estimated correlations between 0.81 and 0.87 (Wechsler, 1955, 1981). Test-retest reliability

was found to be between 0.8 and 0.9 (Matarazzo and Herman, 1984). Arithmetic scores are of only mediocre value as measures of general ability in the population at large, but do reflect concentration and "ideation discipline" (Saunders, 1960a). Arithmetic performance becomes more dependent on memory with increasing age. Arithmetic performance may suffer from poor early school attitudes or experiences (Lezak, 1995). In factor analytic studies, the highest loading is on a freedom from distractibility factor (Kaufman et. al., 1991). Arithmetic is not a good measure of verbal ability. Left parietal (McFie, 1975) and left temporal (Long and Brown, 1979) lesions were shown to affect performance on the test. On PET scans the left hemisphere and to a lesser extent right frontal areas show up (Chase et al., 1984). Lowered arithmetic scores would lead the examiner to suspect immediate memory and concentration problems and raise questions about verbal functioning, but does not necessarily reflect the patients' arithmetic skills (Lezak, 1995).

3.5.2.1. Data generated: Arithmetic

WAIS-R Arithmetic age adjusted scaled scores were generated.

3.6. SUSTAINED ATTENTION

3.6.1. Continuous Performance Test -Identical Pairs

The continuous performance test (Cornblatt et al., 1988) is not a single measure but a family of measures that share a number of features. These include the rapid presentation of a long series of stimuli, with the requirement that a subject responds whenever a designated target or target sequence occurs in the series. There is a relatively low probability that a target will appear.

The Continuous Performance Test -Identical Pairs version (CPT-IP; Cornblatt et al., 1988) was used in this study, and it is described in detail here, as descriptions of this particular version of the task are not readily available in standard neuropsychological textbooks. The theory behind the CPT-IP and the calculation of the outcome measures is complicated, however these measures are computer generated. It is a cognitively challenging form of the task. In high-risk research more difficult forms of the CPT have provided evidence to suggest that attentional deficits may be

markers for a genetic liability to schizophrenia (Rutschmann et al., 1977; Nuechterlein, 1983; Cornblatt and Erlenmeyer-Kimling 1985; Franke et al., 1994). The CPT-IP is a multidimensional task that systematically varies the type of stimulus, distraction, and stimulus exposure time. It requires identification of identical stimulus pairs within a continuously presented series of stimuli. It has been shown to be a reliable measure of attention (Cornblatt et al., 1988). Research concerned with whether attentional deficits are markers of a genetic liability to schizophrenia, typically involves the testing of clinically unaffected (first degree) relatives of schizophrenic patients, where appropriate experimental measures of sustained attention must meet the following criteria (Cornblatt et al., 1988) 1. be suitable for use across a wide range of ages and clinical states to avoid ceiling or floor effects. 2. show clear differences in patterns of attentional processing between schizophrenic and normal individuals, and 3. be sufficiently sensitive to detect marker deficits, which are expected to be qualitatively similar to the dysfunctions characterising patients but quantitatively more subtle.

Attentional dysfunctions have not been found in children at risk for schizophrenia relative to control children in any of the high-risk studies using the simple X or AX tasks (Asarnow et al., 1977; Cohler et al., 1977; Herman et al., 1977; Cornblatt and Erlenmeyer-Kimling, 1984). Studies using more difficult CPT tasks have consistently reported such deficits (Rutschmann et al., 1977; Nuechterlein, 1983; Cornblatt and Erlenmeyer-Kimling, 1985). The 'Playing Card' version of the CPT (Rutschmann et al., 1977) distinguished children at risk for schizophrenia from psychiatric and normal control children (Rutschmann et al.,1977; Cornblatt and Erlenmeyer-Kimling , 1985) although it was most appropriate for the 7 to 10 year old range (Erlenmeyer-Kimling et al., 1984). Nuechterlein increased the load on perceptual processing, an approach that was also effective for tapping attentional deficits in children at risk for schizophrenia (Nuechterlein, 1983). There are many variants of the CPT around, however the CPT-IP is the only one with well established norms, and is said to be suitable for testing multigenerational families (Cornblatt et al., 1988). It evolved over the course of the New York High Risk Study.

The CPT -IP programme is run in conjunction with the MEL programme (Micro Experimental Laboratory; Schneider, 1988). Subjects were required to respond as quickly as possible whenever two identical stimuli were presented in a row, by depressing a designated key and releasing it. Six different conditions were presented to each of the subjects in addition to a practice session consisting of 50, 3 digit numbers. They included one condition of 4 digit numbers and one of nonsense shapes. In these two initial conditions stimuli were flashed on the screen at a constant rate of 1 per second, with a stimulus 'on' time of 50 msecs and 950 msecs of blank screen. Each condition consisted of 150 trials. Numbers were presented first then shapes, these two conditions are referred to as fast no distraction conditions. The second two conditions, again 4 digit numbers and non-sense shapes, were presented in an identical manner except that visual and auditory distractions were added. For the distracted numbers condition the first 50 numbers were degraded, looking overlapped, during the second set of 50 a tape was played in the background while the numbers appeared without visual distraction, and in the final set of 50, white noise in the form of asterisks were flashed around the numbers.

In the shapes condition, the first 100 shapes were accompanied by auditory distraction, a film soundtrack was played in the background, and the final 50 shapes were presented in the presence of white noise identical to that in the numbers condition. The stimuli were presented for the same amount of time as in the first two conditions. These conditions are known as fast distraction numbers and fast distraction shapes. In the final two conditions, again, one numbers and one non-sense shapes, the stimuli are presented without distraction with an on screen time of 150 msecs and a blank screen time of 850msecs. The stimuli are presented at a rate of one per second, but this time they appear to be appearing at a slower rate. These two conditions are referred to as slow numbers and slow shapes. The numbers are considered to be essentially verbal. The non-sense shapes were designed to be resistant to verbal labelling and to be processed holistically, being primarily spatial stimuli. After completing each distraction condition subjects were asked a series of questions with multiple choice answers, about the content of the background story.

(Questions ensured subjects were processing the auditory distraction and served as a secondary performance measure in a type of dual task paradigm). Of the 150 stimuli in each condition, 28 are target trials and require a response (2 identical stimuli in a row), 26 are catch trials, (the stimulus presented is very similar but not identical to the previous one), catch trials are also called 'colds'. There are 96 filler trials, responses to which are classed as random errors, or commission errors.

Performance was measured on 5 different indices. 1). Correct detections or hits (responses to target trials). 2). False alarms (responses to catch trials). 3). Random errors (responses to filler trials) converted to natural logarithms. Also signal detection indices were generated, 4). d' and 5). log β. Signal detection indices have been used with increased frequency to separate out declines in sensitivity (d') or attentional capacity from shifts in response style or tendency to over-respond versus under-respond (β) (Cornblatt et al., 1988). Both are calculate as outlined by Rutschmann et al., (1977) and summarised below. Rutschmann et al., (1977) referred to the likelihood ratio criterion Lx, which is the same as log β in this study. The index of discriminability d' is generated from assessing the degree of overlap between the frequency distribution of the effects generated by the "noise plus signal" [hit] trials and that generated by the "noise alone" [cold] trials. The greater difficulty the subject has in discriminating between the two types of trials the greater the degree of overlap. Signal detection theory assumes that performance on a measure such as the CPT is a function of the discriminability of the stimuli and the response criterion adopted by the subject. The index d' is the distance between the means of these two frequency distributions, expressed in standard deviation units, and is estimated from the conditional probabilities of "hits" and "false alarms". The random error score is based on the proportion of responses to filler trials out of the total number possible (n=96 for numbers and shapes).

The (log β) is a measure of response bias for log β <1.0 the subject has a risk taking criterion and is biased toward button pressing i.e. toward reporting hits. For log β >1.0 the subject is cautious and is biased toward responding i.e. toward reporting colds. When log β =1.0 there is no bias. The assumptions used for computing d' and

log β were that the frequency distributions, density functions, of the "colds" and of the "hots" were normal and of equal variance and that the subjects log β would not vary within a block of trials. An optimal Log β of 1.0 is associated with equal apriori probabilities of occurrences of hits and colds, equal values for hits and correct rejections, and equal costs for false alarms and misses. The calculation of the signal detection indices requires making many statistical assumptions, which may or may not hold for different populations and are difficult to assess. Rutschmann et al., (1977), predicted that if findings on the CPT reflect early developmental disturbances to the extent that such disturbances are continuous with information processing dysfunctions in patients with schizophrenia, one would expect a subgroup of the HR group to be responsible for any group effects. They also predicted that differences between HR and controls would exist prior to the overt clinical symptoms of schizophrenia and that these differences would be due to differences in d', measuring sensory capability, rather than in the response bias measure, log β, which reflects the effects of set, attitude and/or motivation. Differences in motivation or in cooperativeness between the groups would yield differences in log β rather than in d'.

Cornblatt et al., (1988) found that in a normal sample, distraction significantly affected d' and marginally affected log β, they found significant age by log β interactions. The interpretation was that adults showed little change in response style under distraction but adolescents were conservative responders under distraction. In remembering the story details the adolescents did significantly better than adults. They also found in this normal sample, that for d', the sample as a whole were superior on shapes relative to numbers. There were age by stimulus interactions also, the results for d' and ln randoms summed across distraction conditions showed that for adults there was very little difference in the way numbers and shapes were attended to. Adolescents were better at shapes. Log β did not show such a pattern suggesting that the differences between the groups were due to true differences in processing capacity and not just to different response styles due to age. Factor analysis suggested the independence of numbers and shapes, possibly reflecting independent processes. Cornblatt et al., (1988) found heritability estimates bases on mid-parent-mid child regressions and sibling correlations for d' were 39% for

numbers and 49% for shapes. Heritabilities for both log β factors were essentially zero. There was evidence for test re-test reliability, but also for a practice effect. However this does not imply a ceiling effect with repeated testing. Log randoms were not reliable over time, and random errors may be very low. Distraction tended to improve adolescent performance while not really affecting adult performance. They found that children and adolescents appear to attend to spatial input more efficiently than to verbal information. During adulthood both types of material appear to be handled equally well.

Three questions to be answered:

1. Is there a deficit in sustained attention between the groups?

This question was answered by analysing the results of condition one and condition two, fast no-distraction numbers and fast no distraction shapes. Using both conditions it can be checked if the deficit involves both verbal and spatial processing.

2. Is there evidence of abnormal distractibility?

This question was answered by analysing the results of condition three and four, fast distraction numbers, and fast distraction shapes. Both conditions are a repeat of the previous two with one parameter change, the presence of distraction.

3. Is there a deficit in speed of processing?

This question was answered by analysing the results of condition five and six, slow no-distraction number, and slow no-distraction shapes. The assumption being that the longer stimulus exposures enables abnormally slow individuals to more completely process the available information and thus be expected to improve performance levels. Normal subjects should show little advantage by this manipulation.

3.6.1.1. Data generated: CPT-IP

Log randoms, log beta, and d' for 6 conditions, fast no distraction numbers and shapes, fast distraction numbers and shapes, and for slow no distraction numbers and shapes.

3.7. Verbal ability and Language

3.7.1. Token Test

The token test is a test of receptive language function. The description here is based on that of Spreen and Strauss (1991). The test consists of tokens, circles and squares, large ones and small ones. There are five different coloured tokens including red, blue, green, yellow and white. There are 4 rows of five tokens, large circles, large squares, small circles, and small squares. In each row there is one red, blue, green, yellow and white token. The characteristic of the test material is such that when all 20 tokens are present it is not enough to use a single word in order to identify a particular token, at least three specific words are required e.g. small white circle, large yellow square. If only the large tokens are presented, two specific words, a noun and a colour adjective are used. To test for aphasia commands must be given in non-redundant form, in such a way that the understanding of every single word of the sentence becomes indispensable to the correct performance of the order. It must be made impossible for the hearer to deduce or to reconstruct any word he may miss by following the clues contained in the words preceding or following it. None of the qualifying words is redundant each must be decoded correctly in order to choose the right token.

As outlined by Spreen and Strauss (1991) the test is built up of five parts, commands are expressed in an elementary grammatical and syntactic form; verb; object. The fifth part of the test is made more difficult by introducing grammatical particles or other more complex syntactic structures, the exact understanding of which is necessary to correctly perform. Before starting one must be sure that no agnostic disturbances as far as form and colour recognition is concerned are present and that the patient understands the meaning of the words 'circle' and 'square'.

This version of the token test is from the Compendium of Neuropsychological Assessments (Spreen and Strauss, 1991). It forms part of the Neurosensory Comprehensive Examination for Aphasia (Spreen and Benton, 1969, 1977) and is suitable for adults and children. It consists of 39 commands increasing in length and difficulty. The scoring is sensitive to even minor impairments of receptive language.

Spellacy and Spreen, (1969), reported a correct classification of 89% for unselected aphasics and 72% for non-aphasic brain damaged patients using a cut-off score of 156 (Maximum score=196). It has been suggested that impairment on the Token test and similar perceptual tasks in aphasics reflects a general cognitive rather than a language specific deficit.

3.7.1.1.Data generated: Token Test

Total token test score.

3.7.2. Vocabulary

"Vocabulary level has long been recognised as an excellent guide to the general mental ability of intact, well socialised persons" (Lezak, 1995). The WAIS-R Vocabulary subtest is the most common vocabulary measure used. Subjects are asked the meanings of 35 words in all. The test continues until the subject has failed 5 in a row or until the end of the test. A score of 1 or 2 points is awarded for each correct answer, depending on its appropriateness. The score represents both the extent of recall vocabulary and the effectiveness of speaking vocabulary. Age effects have been noted on the test (Wechsler, 1955, 1981) but education affects vocabulary scores to a much greater extent (Malec et al., 1992). In older people, typically with poorer education, urban dwellers were found to do better on the task (Kaufman et. al., 1988). Sex differences are negligible (Kaufman et. al., 1991). Early socialisation experiences tend to influence vocabulary development more than schooling and vocabulary score is more likely than information or arithmetic, for example, to reflect the patients socio-economic and cultural origins and be less affected by academic achievement or motivation (Anastasi, 1988). Test-retest correlations range from 0.78 to 0.84 (Ryan et. al., 1985), except in the case of schizophrenia with an estimate correlation of only 0.38 (Goldstein and Watson, 1989). Factor analytic studies locate the Vocabulary subtest on a verbal factor, and also on a measure of general intelligence (g). On PET scans, increased glucose metabolism occurs predominantly in and around the left temporal lobe while the test is taken and small metabolic increases have been shown in the right hemisphere (Chase et al., 1984).

3.7.2.1. Data generated: vocabulary

Age adjusted scale scores.

3.8. Learning and Memory

3.8.1. Rivermead Behavioural Memory Test

This test was developed to provide measures that could be directly related to the practical effects of impaired memory and for monitoring change with treatment for memory disorders (Wilson et al., 1985). It was also designed to have face validity. It includes mostly practically relevant tasks, including measures of immediate and delayed memory recall. There are four parallel versions of the RBMT. Neither age nor gender contributed to the scores for the standardised group (Wilson et al., 1989). About 10% of the variance appeared to be associated with mental ability. Inter-scorer agreement was reported to be 100% (Wilson et al., 1989). Two scores can be calculated, a standardised profile score and a screening score. The standardised profile score may be a more sensitive measure of memory abilities, and both correlate highly with other tests of learning and memory (Wilson et al., 1989). The test development was shaped by clinical experience with memory impaired patients. It does have practical value but with only a 2 or 3 point scoring range it lacks sensitivity at both high and low ends of memory functioning (Leng and Parkin, 1990).

3.8.1.1. Data generated: Rivermead Behavioural Memory Test

A standardised profile score and a screen score were both generated for each person. Also scores for the story, immediate and delayed recall, were examined individually. The story recall, both immediate and delayed was the most challenging aspect of this test for all subjects, and therefore we thought it might be the most discriminating of the subtests.

3.8.2. Rey Auditory Verbal Learning Test and parallel versions

The Rey (1964) and parallel versions were used here as a test of verbal learning. This test measures immediate memory span, provides a learning curve, reveals learning strategies or their absence, elicits retroactive and proactive interference tendencies, also tendencies to confusion or confabulation on memory tasks (Lezak,

1995). It measures both short term and long term retention following a period of distraction by doing another task, and allows for a comparison between retrieval efficiency and learning. It consists of 5 presentations with recall of a 15 word list, one presentation of a second word list, and a sixth recall trial. We examined delayed recall after 20 minutes in this study. It begins as a test of immediate word span recall. List A, consisting of 15 words, which were read out to subjects at the rate of one per second. The subject was instructed to recall as many words as they could remember, in any order. When no more words were remembered, the list was called out again. Subjects were encouraged to provide as complete a list as possible, so that words recalled on previous trials should be recalled again on subsequent trials. A second list B was called out after 5 trials on list A, with the same instructions. For trial VII the subject was asked to recall as many words from the first list as possible. After a 20 minute delay, (during which the subject completed the HSCT and the Token test) the subject was requested to recall as many words as possible from the first list. Subjects were then presented with a piece of paper listing 50 words, containing all the words from list A, all the words from list B, but also words that were never called out, but had phonemic and semantic similarities to the true list words. The subject was requested to identify any words that were called out, indicating whether they were from list A or list B, or identifying them as being from one of the lists where the subject was unsure exactly which list they came from.

Recognition scores below 13 are relatively rare among intact persons under the age of 55 (Lezak, 1995). Due to any possible practice effects, the Crawford and Jones-Gotman versions of the AVLT were given at subsequent assessment periods. Most studies have found that immediate recall (i.e. supraspan) runs within the range of 6.3 and 7.8 for persons under 70 (Lezak, 1995). The change in number of words recalled from trial I to trial V shows the rate of learning and reflects little or no learning if the number of words recalled on later trials is not much more than the number remembered on trial I. A range of 12 to 14 for trial V is often quoted for studies of normal subjects, and recall on trial VI immediately following trial the administration of trial B, generally falls an average of 1.5 -2 words below trial V with little lost between VI and VII (Lezak, 1995). Trial B is like trial I in that it measures recall of

a 15 word supraspan and typically generates scores similar to trial I. Age is important, education and verbal facility as measured by vocabulary (WAIS-R) and general mental ability also contribute significantly to performances on this test (Bolla-Wilson and Bleecker, 1986; Wiens et al., 1988). Factor analytic studies of AVLT revealed a high learning measure. The supraspan measure, trial I, reflects its large attentional component in negligible correlations with learning measures (Macartney-Filgate and Vriezan, 1988).

3.8.2.1. Data generated: Auditory Verbal Learning Test

The score for each trial was the number of words recalled. The total number of words recalled across trials I to V were totalled also. The number of words recalled in the delayed recall trial, after 20 minutes, was recorded, as was the number of correctly recognised words from each list.

3.8.3. Visual Reproductions

The Visual Reproduction's sub-test (Wechsler Memory Scale-Revised; Wechsler, 1987) was administered, both immediate recall and after a 20 minute delay. The test consists of 4 drawings, three containing a single figure and one with two designs one containing three, the other containing two geometric figures. The maximum score achievable is 41 points. The subject was given 10 seconds exposure time to the picture to facilitate memorising it. After 10 seconds the card was removed and the subject had to draw the design from memory. Such tasks are particularly sensitive to right hemisphere damage regardless of site (McFie, 1960). Education effects exist for both immediate and delayed trials (Ardila and Rosselli, 1989). Educationally deprived people may do poorly on this test. For this test and inter-rater reliability coefficient of 0.97 was reported with scoring differences of 4 points or less and an average differences between 2 and 1.5 scores. (McCaffrey et al., 1992). This test correlates more significantly with tests involving predominantly visuospatial problem solving and visual memory (Lezak, 1995).

3.8.3.1. Data generated: Visual Reproductions

Total scores (maximum of 41) for the immediate and delayed recall trials were analysed separately.

3.9. Lateral preferences

3.9.1. Hand Preferences

Hand preferences were measured using a scale, which combined both the Edinburgh Handedness Inventory (Oldfield, 1971) and the Annett Handedness Questionnaire (Annett, 1970). This new scale comprised 15 items to assess hand preference and a further two items to assess eye and foot preference. Subjects were requested to demonstrate which hand they would use to carry out each of the tasks. Appropriate props were provided for the subjects. The hand used to do the task was recorded. The tasks were repeatedly administered in a quasi-random fashion (three times in total) so that stability and consistency of response could be measured (Nelson et al., 1993). In addition each of the subjects were requested to give verbal responses as to which hand they would use to do each tasks; right hand always, right hand mostly, either, left hand mostly, left hand always.

3.9.1.1. Data generated: Handedness measures

Edinburgh Handedness Inventory

A quantitative and qualitative measure of handedness was derived from the EHI. A laterality quotient (Oldfield, 1971) was calculated for each individual. The laterality quotient (L.Q.) was calculated according to the formula:

$$L.Q. = \frac{E\,x(i,R) - E\,x(i,L)}{E\,x(i,R) + E\,x(i,l)}$$

Where X(i,R) and X(i,L) are the number of +'s for ith item in the Right and Left columns respectively (Oldfield, 1971).

The L.Q. is a quantitative measure of handedness. The L.Q. ranges from -100 to +100. Participants with a L.Q. of -100 are strong left handers and participants with a

L.Q of +100 are strong right handers. From this the qualitative measure of handedness can be derived e.g. a 90% cut-off criteria was chosen, and participants were classified as right handed if the L.Q. was greater than or equal to +90, as left handed if the L.Q was less than or equal to -90, and as mixed handed if the L.Q. was less than +90 and greater than -90.

Annett Handedness Scale (1970).

In classifying handedness using the Annett method, a qualitative measure of handedness was derived. The scoring was derived from verbal recall of the items. Responses of 'either hand' to complete a task are noted but are not used as a criterion of non-right preference. The subjects classified as "mixed" handers by Annett in her samples always show a definite preference for the left hand for at least one of the actions when the other responses were always right. This means that if a subject responds that they use the right hand to do most of the tasks but their response to one or more task is 'either hand', the individual is classified as right handed. If they respond mostly as 'left hand' but also respond to one or more as 'either hand' they are classified as left handed. Only when at least one of the items, is carried out by the opposite hand to that carrying out all other tasks, is the person categorised as mixed handed.

Analyses were carried out separately for the two scales. Also each scoring system was applied to each of the scales as a measure of how much hand preferences differed in response to the different scoring criterion employed. The percentage of individuals categorised as right/left or mixed handed by each of the outlined methods were compared across groups. From the repeated demonstration of tasks, the stability of hand preference was calculated and compared across groups. Also as the hand preference questionnaire was repeated at 18-month intervals the stability of hand preferences across time was calculated.

3.9.2. Foot and eye preference

Eye preference was evaluated by asking the individual to look through a small hole in a piece of A4 size paper and by rolling up a piece of paper and asking the person

to look through it as though it were a telescope. Foot preference was observed when the subject kicked a football across the room and also by verbally responding to the question 'which foot do you kick with?'. Each subject was asked if they had a family history of left handedness.

3.9.2.1. Data generated: Foot and eye preference

A qualitative measure was derived for foot and eye preference. In the verbal recall trial, participants were classified as right footed or right eyed if they responded right always; as left footed or left eyed, if they responded left always; mixed footed or mixed eyed, if they did not have a consistent preference for either right or left. In the demonstration trials the preferred hand was noted and recorded.

CHAPTER FOUR: EXPLORATORY DATA ANALYSIS

4.1.Exploratory data analysis

4.1.1. Neuropsychological test results (excluding the CPT)

The data were collected by two assessors (Majella Byrne, MB, Richard Cosway, RC) and scored by three people (MB, Masimo Tarsia, MT, RC) due to the time consuming nature of this task. Scoring ranged from simply adding up numbers to produce a total score, to scoring material according to established systems, but with an element of subjective judgement. Inter-rater reliability was examined between two of the raters (MB and RC) for three tests requiring subjective judgement and interpretation for scoring. It was predicted that inter-rater reliability would be high as all the tests are standardised and are used broadly in clinical and experimental settings and provide good guidelines for scoring.

All data when collected, were scored and entered into the computer as an 'spss.sav' file. The data were checked for logical errors. Frequency distributions were produced for each variable and any data points outside the allowed range of values (data entry errors) were corrected.

Three tests requiring some element of subjective judgement in the scoring of the test were selected for the inter-rater reliability exercise. These included the visual reproductions subtest of the WMS-R, both the immediate (n=7) and delayed conditions (n=7), the immediate story recall from the Rivermead Behavioural Memory Test (n=8), and the National Adult Reading Test (NART; n=8). Subjects were randomly selected from the high-risk group files, different subjects were selected for the different tests. As expected, there was very close agreement between the two raters, and the inter-rater agreement was deemed acceptable. The correlations are presented in Table 4.1. Dependent t-tests revealed significant differences between raters on the visual reproductions task. The mean difference was 1 point, with a small associated standard deviation. This provides no cause for concern as it has been reported that in the presence of good inter-rater reliability (0.97) the differences between raters is on average 2 points. (McCaffrey et al., 1992).

Table 4.1. Inter-rater assessment of the three tests.

	Visual reproduction 1 n=7	Visual reproduction 2 n=7	RBMT story immediate recall n=8	National Adult Reading Test n=8
Pearson's r	**0.96**	**0.97**	**0.98**	**0.99**
P, 2-tailed sig.	0.001	0.001	0.001	0.001
Spearman's rho	**0.95**	**0.95**	**0.96**	**0.95**
P, 2-tailed sig.	0.001	0.001	0.001	0.001
Mean difference (sd) Raters RC-MB	-1.0 (0.82)	-1.0 (1.15)	-0.12 (0.88)	0.25 (1.39)
Dependent t (p)	t=-3.22 (P<0.01)	t=-2.32 (P<0.05)	t=-0.51(NS)	t=0.31 (NS)

4.2. Methods of Data Analysis

It was decided that the data analysis should be conducted in three stages.

1). The first stage would be to conduct univariate analyses (using analysis of variance and analysis of covariance techniques) for each variable comparing the three groups (high-risk, control, patient) in an attempt to identify any, even subtle, differences between the groups.

2). The second stage would be to take a data reduction approach. By factor analysing the neuropsychological test scores it would be possible to reduce the quantity of data to a more manageable proportion, thereby circumventing some of the problems that arise from multiple comparisons and multicollinearity in the data.

3). The third approach would be to standardise all the test scores, using the control group data as the normative data. This would allow the computation of composite scores for specific domains of function (Table 3.1), with the effect of reducing the volume of data to be analysed. The standardisation of the scores allows each test result to be viewed on the same standardised scale, allowing direct comparisons to be made across all tests. Also the standardised scores could be corrected for the effects of confounders.

In order to conduct the above analyses a number of steps were taken to prepare the data. The choice of the most appropriate statistical test to be used was dictated by the properties of the data to be analysed, the number of individuals for whom data were available, the type of questions to be asked of the data, and other considerations e.g. data distribution and independence of observations. In order to use more robust parametric data analytic techniques a number of criteria must be fulfilled. The data

must consist of independent observations, come from populations which have similar variances, be measured at least on an interval scale, and the observations should have a normal distribution (Siegel and Castellan, 1988). Although some of the tests are known to be normally distributed in the general population (e.g. the WAIS-R) it was still necessary to investigate the distribution of the test scores in each group as the data should also be consistent with the assumption of normality (Altman, 1991, page 143). The requirement for the use of parametric tests is that the data come from an underlying normal distribution, in practice if the sample data deviate from normal greatly it is possible that the results may not be valid. Where it is possible to transform the non-normal data to a normal distribution the analysis can be greatly simplified (Ott, 1993, page 454). It is also important to look at the data distribution of the variables in order to be able to identify any outlying observations, "it is important to detect such errors if possible, partly because they are likely to invalidate the assumptions underlying standard methods of analysis and partly because gross errors may seriously distort estimates, such as mean values" (Armitage and Berry, 1994, page 399-400). Transformation of the data reduces the influence of outlying points. The scores from the Hayling Sentence Completion Test are, by design, not normally distributed and so require a non-parametric analysis. It is also true that the parametric tests are fairly robust against deviations from normality however it was felt to be important to adopt a cautious approach in this instance and to investigate the distributions of the data, it is also a practice recommended by medical statisticians (Altman, 1991).

4.3. Step 1: Assessing normality

The distribution of each variable for each of the three groups (high-risk, control, and patient) was investigated for normality. Normality was assessed using the *'Explore'* function in SPSS 8.0. Histograms, normal probability plots (Q-Q plots), and detrended normal probability plots (Q-Q plots) were produced, along with formal tests for normality including; the Kolmogorov-Smirnov test with Lillifors significance level and the Shapiro-Wilks test for samples of less than 50 observations. The normal probability plot (Q-Q Plot) plots the quantiles of a variables distribution against the quantiles of the normal distribution. If the variable distribution matches the given theoretical distribution then the points will cluster along a line. The Q-Q Plot is a useful visual tool

for assessing how far each point deviates from normality. Non-normality is usually more marked in the tails of the distribution and the normal probability plots are useful in detecting outliers, which will be situated away from the line. The detrended probability plots should reveal random deviation about the line and no patterns should be apparent if the data is normally distributed. An example of each type of plot is given in Figure 4.1 for a non-normally distributed variable and in Figure 4.2 for a normally distributed variable.

Figure 4.1. Examples of Plots for a non-normally distributed variable.

Fig 1a. Histogram of total Hayling errors

High risk group

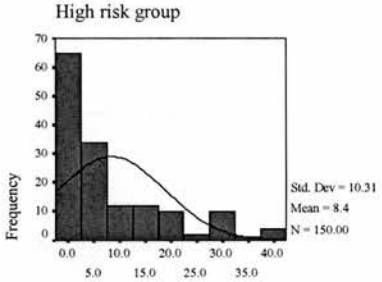


Fig 1b. Normal Q-Q Plot of total Hayling errors

High risk group

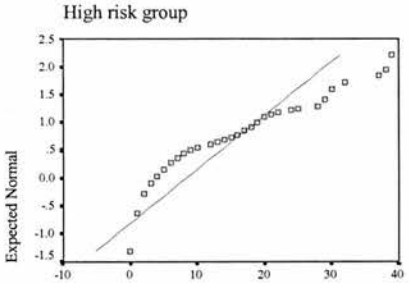


Fig 1c. Detrended Normal Q-Q Plot of total Hayling errors

High risk group

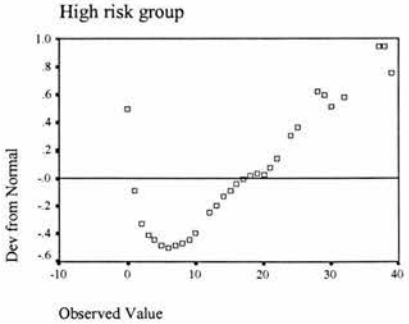


Figure 4.2. Examples of plots for a normally distributed variable.

Fig 2a. Histogram of NART full Scale I.Q.

High risk group

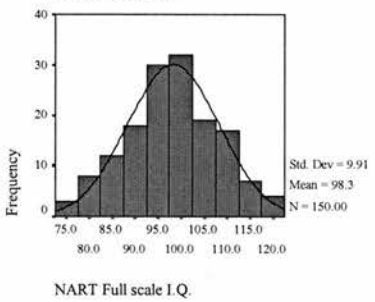


Fig 2b. Normal Q-Q Plot of NART full scale I.Q.

High risk group

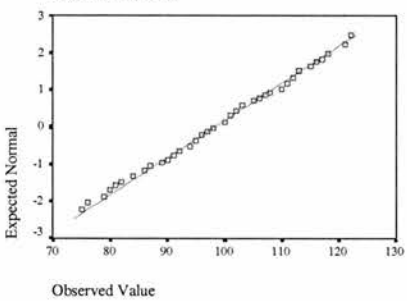
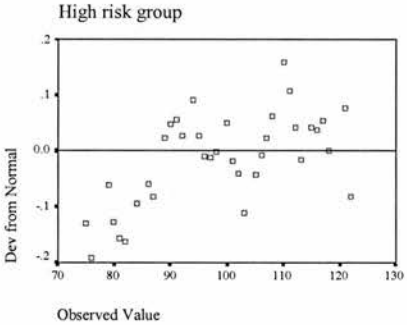


Fig 2c. Detrended Normal Q-Q Plot of NART full scale I.Q.

High risk group



The formal tests for normality, the Kolmogorov-Smirnov, and the Shapiro-Wilks test, calculate the probability that such a value would be obtained in a sample if the population had a normal distribution. If the probability is large enough, we can conclude that the data are reasonably near a normal distribution (Altman, 1991).

A combination of plots, formal tests and subjective judgement was implemented in order to assess each variable for normality. It was necessary to exercise subjective judgement in the assessment of normality (as is standard statistical practice) allowing some variables with small deviations from normality, thought not to be critical, to be

accepted as normal as the statistical tests are very sensitive to even subtle deviations from normality even when these are not likely to violate the assumptions of parametric tests. All tests and many individual elements of a test (e.g. subtests of the WAIS-R, and trials on the Rey Auditory Verbal Learning Test) were subjected to the normality checks in addition to the composites of these elements (total test scores). In Table 4.1 each variable is listed, the final decision of whether or not it was normal and the kind of correlation to be used in further analysis is given.

Table 4.2. Results of the check for normality for round one Neuropsychological test variables.

Neuropsychological test score	Final decision about distribution	Correlation co-efficient used
NART	Normal	Pearson's r
WAIS-R INFORMATION	Normal	Pearson's r
DIGIT SPAN	Normal	Pearson's r
VOCABULARY	Normal	Pearson's r
ARITHMETIC	Normal	Pearson's r
COMPREHENSION	Normal	Pearson's r
SIMILARITIES	Normal	Pearson's r
PICTURE COMPLETION	Normal	Pearson's r
PICTURE ARRANGEMENT	Normal	Pearson's r
BLOCK DESIGN	Normal	Pearson's r
OBJECT ASSEMBLEY	Normal	Pearson's r
DIGIT SYMBOL	Normal	Pearson's r
VERBAL IQ	Normal	Pearson's r
PERFORMANCE IQ	Normal	Pearson's r
FSIQ	Normal	Pearson's r
VERBAL FLUENCY 'F'	Normal	Pearson's r
VERBAL FLUENCY 'A'	Normal	Pearson's r
VERBAL FLUENCY 'S'	Normal	Pearson's r
ANIMALS	Normal	Pearson's r
STROOP	Normal	Pearson's r
SPOT THE WORD	Normal	Pearson's r
SPEED OF COMPREHENSION	Normal	Pearson's r
SCOLP	Normal	Pearson's r
TOKEN TEST, TOTAL	Not normal, no suitable Transformation	Spearman's Rho
RAVLT I	Normal	Pearson's r
RAVLT II	Normal	Pearson's r
RAVLT III	Normal	Pearson's r
RAVLT IV	Normal	Pearson's r
RAVLT V	Not normal, no suitable transformation	Spearman's Rho
RAVLT VI	Not normal	see below
RAVLT RECALL	Normal	Pearson's r
RAVLT Delayed recall	Not normal, no suitable transformation	Spearman's Rho
RAVLT Words recognised from list A	Not normal, no suitable transformation	Spearman's Rho

Neuropsychological test score	Final decision about distribution	Correlation co-efficient used
RAVLT Words recognised from list B	Normal	Pearson's r
RAVLT TOTAL (I-V)	Normal	Pearson's r
RAVLT word recognition errors	Not normal	see below
HAYLING ERRORS A	Not normal, no suitable transformation	Spearman's Rho
HAYLING ERRORS B	Not normal, no suitable transformation	Spearman's Rho
TOTAL HAYLING ERRORS	Not normal, no suitable transformation	Spearman's Rho
HAYLING TIME B	Not normal	see below
HAYLING TIME B-A	Not normal, no suitable transformation	Spearman's Rho
HAYLING TIME A	Not normal	see below
RBMT Standardised score	Not normal, no suitable transformation	Spearman's Rho
RBMT Screening Score	Not normal, no suitable transformation	Spearman's Rho
RBMT Story immediate	Normal	Pearson's r
RBMT Story delayed	Normal	Pearson's r
VERBAL FLUENCY 'FAS'	Normal	Pearson's r
DIGITS FORWARDS	Normal	Pearson's r
DIGITS BACKWARDS	Normal	Pearson's r
Visual Reproductions Immediate	Not normal	see below
Visual Reproductions Delayed	Not normal	see below
Rey trial v-trial I	Normal	Pearson's r
Rey trial I- list B	Normal	Pearson's r
Rey trial v-trial vi	Normal	Pearson's r
Rey trial vi- trial I	Normal	Pearson's r
Stroop condition 3-condition 1	Normal	Pearson's r
WMS-R VR1 – WMS-R VR2	Normal	Pearson's r
Variables transformed to normal	**Transformation to normal**	
RAVLT VI	**Squared**	Pearson's r
Hayling Time A	**Ln(Ln)**	Pearson's r
Hayling Time B	**Ln(Ln)**	Pearson's r
Visual Reproductions Immed.	**To the power of 4**	Pearson's r
Visual Reproductions Delayed	**To the power of 4**	Pearson's r
RAVLT word recognition errors	**Square root**	Pearson's r

For a variable to be considered normally distributed it was necessary that it be displayed in all groups, high-risk, patient, and controls. The variables are listed above for all groups together. It can be seen from Table 1 that in many cases normality was not evident. It was decided to transform the non-normal data to a normal distribution by using a power transformation on the data and re-running the

normality checks on the transformed variable. As can be seen from Table 4.2 certain variables were not normally distributed and suitable transformations could not be found. The analysis of these data were therefore conducted using non-parametric statistical methods. Six variables, listed at the end of the Table, were successfully transformed. The type of power transformation made is also listed. The transformations preserve the order of data, so values larger in the original scale, will be larger in the re-expressed scale, but the spacing will change. A particular power transformation either compresses the scale for larger data values more than the smaller ones, or does the reverse (e.g. see Ott, 1993, 454-460). For data that are positively skewed, transformations, which reduce the larger data values more than the small ones need to be used, such as log transformations. For data that are negatively skewed, transformations, which increase the larger values more than the smaller ones are necessary, for example, squaring or cubing the distribution (Ott, 1993). In Table 4.3, presented in Appendix 2, the means and standard deviations, the median and the 25^{th} and 75^{th} percentiles are given for each of the variables. They are presented to provide information about the data distributions. Information about the transformed data is given at the end of the Table.

4.4. Step 2: Preparation for Factor Analysis

Due to the large number of data points for each person a factor analysis was considered to be an appropriate method of reducing the data. A few problems existed with the data set and these had to be rectified prior to continuation.

Due to the large battery of neuropsychological assessments, not all individuals were able to complete the entire battery due to a variety of reasons, mostly due to time constraints, and sometimes patients had difficulties in concentrating for so long. If for example 30 variables were subjected to factor analysis and if one individual had one missing value on any of the variables, they would be excluded from the factor solution, thus very much weakening our interpretation. There are methods available for dealing with such missing data points and for imputing such values. Often the mean of the population is used for this purpose, however it was felt that if the data points could be accurately predicted by the individuals scores on other tests, that this

would be more likely to reflect the individuals (unknown) true score. The first step was to compute a matrix of correlations for each group to evaluate the relationship of each variable with every other variable. The type of correlation used was that outlined in Table 2, with Pearson's r used for normal data and Spearman's rho used for non-normal data. The aim was to identify variables closely related to the variable to be imputed, and to construct linear predictors to allow for accurate prediction of the data. This was restricted to variables with a normal distribution. Where variables were not normally distributed missing values were replaced by the median of the group. The correlation matrix for each group, controls, patients and high-risk subjects, along with significance levels are presented in Appendix 2, matrices 4.1, 4.2, and 4.3. The imputed values were used only in the factor analysis, only actual values were used in the other analyses. The number of missing data points, in the combined sample, for which data imputation was necessary, ranged from a minimum of 7% (17/235 missing data points for WAIS-R variables) to a maximum of 14% (33/235 missing data points for the Stroop test).

The prediction equations were derived from a series of linear regression models. The linear predictors for the variables are given in Table 4.4. In all cases the predicted value, $\hat{Y}$= a constant value + the slope* (the independent predictor variable). All of the regression models resulted in a single predictor variable (independent variable). This variable was the variable most highly correlated with the dependent variable. All regression models were statistically significant.

In order to test the accuracy of the linear predictors, a random sample of 5% of cases from each of the three groups was selected and deleted from the data set. The Linear predictors were then calculated. By removing a small sample, the linear predictors could be used to predict the values of these subjects where the true values were known, and the discrepancy between the actual and predicted values could be evaluated to test the usefulness of the models. These subjects were included in the factor analysis. The observed and predicted values, and the discrepancies for the random sample are presented in Appendix 2, 4.4, along with the group mean for each of the variables. The linear predictor gave approximations closer to the true observations than would have

been achieved by substituting the mean in most instances. All three groups were factor analysed together reducing the number of variables was the aim of the exercise. The factor analysis is outlined in chapter 5.

Table 4.4. Linear predictors for each group for the imputation of scores for factor analysis

VARIABLES TO BE PREDICTED	CONTROLS	HIGH RISK	PATIENTS
Verbal fluency 'F'	$\hat{Y}$ =6.661+0.782 (vocabulary)	$\hat{Y}$ =5.002+0.933 (vocabulary)	$\hat{Y}$ =4.765+0.670 (vocabulary)
Verbal fluency 'A'	$\hat{Y}$ =2.934+0.745 (digit symbol)	$\hat{Y}$ =5.82+0.497 (digit symbol)	$\hat{Y}$ =2.781+0.599 (similarities)
Verbal Fluency 'S'	$\hat{Y}$ =4.242+0.108 (FSIQ)	$\hat{Y}$ =2.265+0.125 (FSIQ)	$\hat{Y}$ =-6.187+0.194 (FSIQ)
FAS	$\hat{Y}$ =12.629+0.269 (FSIQ)	$\hat{Y}$ =-6.048+0.451 (FSIQ)	$\hat{Y}$ =-12.315+0.46 (FSIQ)
NART	$\hat{Y}$ =78.875+2.886 (vocabulary)	$\hat{Y}$ =73.028+3.009 (vocabulary)	$\hat{Y}$ =67.654+3.684 (vocabulary)
Animals	$\hat{Y}$ =-5.534+0.226 (FSIQ)	$\hat{Y}$ =-3.616+0.197 (FSIQ)	$\hat{Y}$ =-6.667+0.220 (FSIQ)
Stroop	$\hat{Y}$ =30.304-0.750 (speed of comprehension)	$\hat{Y}$ =33.166-0.863 (speed of comprehension)	$\hat{Y}$ =36.735-0.195 (speed of comprehension)
Spot The Word	$\hat{Y}$ =4.429+0.714 (vocabulary)	$\hat{Y}$ =3.094+0.766 (vocabulary)	$\hat{Y}$ =2.085+0.949 (vocabulary)
Speed Of Comprehension	$\hat{Y}$ =5.091+0.65 (digit symbol)	$\hat{Y}$ =5.339+0.574 (digit symbol)	$\hat{Y}$ =4.223+0.564 (digit symbol)
SCOLP	$\hat{Y}$ =5.869-0.629 (digit symbol)	$\hat{Y}$ =1.900-0.347 (digit symbol)	$\hat{Y}$ =7.172-0.831 (digit symbol)
RAVLT VI	$\hat{Y}$ =-56.89+17.615 (RAVLT delayed recall)	$\hat{Y}$ =-54.725+17.235 (RAVLT delayed recall)	$\hat{Y}$ =-39.877+15.955 (RAVLT delayed recall)
Visual Reproductions Immediate Recall	$\hat{Y}$ =879223.8+91415.74 (block design)	$\hat{Y}$ =155008.8+136299.2 (block design)	$\hat{Y}$ =188207.9+122800.7 (block design)
Visual Reproductions Delayed Recall	$\hat{Y}$ =4325447.8+99170.305 (block design)	$\hat{Y}$ =-285484+148588.1 (block design)	$\hat{Y}$ =-417388+133341.2 (block design)

4.5. Step 3: Standardising the test scores

Another popular and useful method of dealing with such data is to standardise all the variables to the same scale and to then compute composite scores for the different domains of function (domains of function examined by the neuropsychological test battery are outlined in Table 3.1). Then the number of variables can be reduced to a few composite scores. The standard score chosen here was the z-score. Z scores indicate how far and in what direction, an item deviates from the mean of its

distribution, expressed in units of its distribution's standard deviation. Z-scores have a mean of zero and a standard deviation of 1. They are useful for comparing items from distributions with different means and/or different standard deviations. Standardised z-scores were produced for each group. However, the z-scores for the high-risk group and the patient group were computed using the control group mean and standard deviation, using the formula;

$$Z=Xij-X_{(control)} /SD_{(control).}$$

This means that the z-scores represent how far, and in what direction, items deviate from the control group mean, expressed in units of the control groups' standard deviation. Z scores were computed for the individual neuropsychological tests. Composite scores were produced for five domains of function according to Table 3.1. The composite score was calculated as the average of the Z scores for each particular domain. These were:

1. executive function (Hayling errors, time on section A, Stroop incongruous condition, FAS, Animals),
2. mental control/encoding (digits forward, digits backward, arithmetic),
3. perceptual motor speed (digit symbol),
4. language (token test, vocabulary),
5. learning and memory (RBMT, Rey total I-V, Rey delayed recall, visual reproductions immediate and delayed conditions, story immediate and story delayed).

Given the known large effect of IQ on neuropsychological test performance generally, and due to differences between the groups in terms of current and premorbid intellectual function, it was thought necessary to analyse data with and without NART as a covariate. The NART was chosen as the co-variate as opposed to WAIS-R full scale IQ as it is a measure of pre-morbid IQ, and it is likely to be less affected by the development of illness, and illness precursors than measures of current intellectual functioning. A recent meta-analytic review (Heinrichs and Zakzanis, 1998) outlined in the next chapter (section 5.1.2), reported that there was a considerable degree of variability around the NART mean and questioned its reliability as a measure of

premorbid ability. However, other studies have reported that it is a reliable instrument (Nelson, 1982; Crawford et al., 1988; O'Carroll, 1987). When testing subjects who have never been administered an IQ test before, it is really impossible to say whether the measure of 'pre-morbid function' is accurate or not, however, given the known effects of a current schizophrenic illness on cognitive decline (Frith et al., 1991) and the fact that some studies have reported the NART to be a reliable instrument, the use of this instrument as a co-variate in the analyses was deemed to be justified.

There are psychometric problems associated with inferring a group differential ability when the only available measures are of performance (Chapman and Chapman, 1989). Performance varies not only with ability but also with the psychometric properties of the task. Larger differences between groups will be found on tests with greater true-score variance. The authors suggest the need for a matched task design in order to determine the presence of a group differential affect. They provide one solution to the problem of measuring individual differences in differential ability, not requiring matched tasks. They propose the method of using standardised residual scores, which will remove specific extraneous variance measured by the second task. This method has been used in other neuropsychological studies (Saykin et al., 1991, 1994; Faraone et al., 1995). The method was used here in order remove the extraneous variance due to premorbid intellectual functioning, in order to adjust for the group differences on this measure. (We did not attempt to control performance on each test or domain, for performance on others). For observed scores on test A (in this case NART), scores on test B (other neuropsychological variables) are predicted using the regression of B on A and computed on the normal control sample. Then the standardised scores are created using the formula

Z=Observed B-Predicted B /Standard error of the observed scores around the regression line B.A. (control).

Firstly the model was calculated on the control scores, and then on the basis of the model parameters, predicted scores for all groups were calculated. The residuals were calculated by subtracting the predicted scores from the observed values. The residual

scores were standardised for all groups by dividing by the standard error (square root of the mean square error) from the regression model (control data only). This produced standardised scores that were adjusted for NART. They were organised into the above outlined domains of function in exactly the same manner.

4.6. Analysis of the CPT-IP

The CPT-IP generated a large quantity of measures and for this reason it was considered separately to the other tests. As recommended by other researchers (e.g. Cornblatt et al., 1988) three indices were analysed, d'prime, log randoms, and log beta. These measures are defined in detail in Chapter 3. Numbers and shapes conditions were analysed both in the presence and absence of distraction and with and without NART FSIQ as a covariate. These are summary measures of more complicated data and are thought to be the most informative (Cornblatt et al., 1988). Z scores were computed for log beta, d'prime, and log random overall, and separately for numbers and shapes conditions. Normality checks revealed that both d'prime and log beta were normally distributed, however log randoms were not. It was not possible to log this variable as zero was the most frequent value and a further suitable transformation could not be found. These data were subject to multivariate analysis of variance, with and without NART as a co-variate. The method suggested by Conover and Inman (1982) was used for log random values in the covariate analysis. (The CPT-IP measures were standardised in a straightforward, unadjusted manner. Adjustments for NART were made later as it was felt that too many assumptions would have to be made in order to compute the standardised residual scores according to the method of Chapman and Chapman, 1989).

CHAPTER FIVE: NEUROPSYCHOLOGICAL ASSESSMENT OF YOUNG PEOPLE AT HIGH GENETIC RISK FOR SCHIZOPHRENIA, COMPARED TO CONTROLS AND PATIENTS WITH A FIRST EPISODE OF SCHIZOPHRENIA: BASELINE ANALYSIS

5.1 Neuropsychology and Schizophrenia: a summary of the literature

5.1.1. Background

It is well established that the diagnosis of schizophrenia is often accompanied by neuropsychological impairments. There have been numerous reports of generalised deficits in cognitive functioning and in addition there has been some delineation of circumscribed cognitive deficits set against this background of general impairment. However a sizeable proportion of patients with a diagnosis of schizophrenia do not have demonstrable neurocognitive impairments (e.g. Heinrichs and Awad, 1993) and there is much variability in the extent of the deficits among those who do. The classical approach to the investigation of neuropsychological deficits in schizophrenia was driven by the hope that the illness was a manifestation of some underlying brain lesion(s). The increasingly sophisticated field of structural imaging has confirmed that the brains of patients with schizophrenia are not characterised by localised brain lesion(s), although a heterogeneous array of cerebral abnormalities have been identified (Chua and McKenna, 1995) and some appear more consistent than others (e.g. cerebral ventricular enlargement). Also, more patients are classified as abnormal by neuropsychological tests than by scans (Dunkley and Rogers, 1994). The evolution of functional imaging techniques has lead researches to focus, not on specific anatomical sites, but on the functional connections between brain areas, with some promising leads (McGuire and Frith, 1996). While the neuropsychological investigations in schizophrenia have mainly utilised the classical approach, the field of cognitive neuropsychology characterised by the work of Frith and colleagues, has shifted the emphasis away from the search for underlying lesions associated with a general diagnosis of schizophrenia, to the search for detailed cognitive models that can be mapped to brain functioning, with particular emphasis on specific symptom and behavioural profiles of patients. Another promising approach has been to conduct single case studies of patients with a focus on the specific within-patient pattern of illness and deficits (Shallice et al., 1991), helping to avoid the heterogeneity problem. There have been many methodological difficulties and differences in studies conducted in this area. The extent to which the findings are confounded by illness related variables (e.g. failure in education, and negative signs) are not clearly understood.

Despite the methodological difficulties, there is surprising uniformity of results, at least broadly, and most suggest that at least some patients with schizophrenia display a broadly based general deficit in neuropsychological performance and in addition there may be circumscribed deficits in some areas of function, particular candidates being aspects of memory and executive functioning. When and why do these deficits emerge? What do they signify? Are they state (e.g. affected by symptoms and medication) related or enduring traits? Do they progress or remain static over the course of the illness? Do these deficits exist in unaffected family members? Can they be identified as markers for schizophrenia in those who will later develop the illness? These are questions that have dominated the literature investigating the neuropsychological deficits in patients with schizophrenia, in the adult relatives of such patients, and in the offspring of these patients (HR studies) and are some of the issues considered below in the literature summary of the area.

5.1.2.The Profile of Neuropsychological Impairment

Heinrichs and Zakzanis (1998) conducted a recent quantitative review of the literature investigating neurocognitive deficits in patients with schizophrenia, compared to normal controls, using meta-analytic techniques. The authors reported 22 mean effect sizes from 22 meta-analyses of 204 studies investigating differences in global and selective verbal memory, non-verbal memory, bilateral and unilateral motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, language, and interhemispheric tactile-transfer performance. They found that moderate to large effect sizes ($d > 0.60$) were obtained for all 22 neurocognitive test variables and none of the confidence intervals included zero. They concluded that schizophrenia is characterized by a broadly based cognitive impairment with varying degrees of deficit in all domains measured by standard clinical tests. The review was restricted to subjects with DSM III or later, or ICD 9/10 diagnoses and tests were required to have been administered by trained examiners. 509 effect sizes were generated from 7,420 patients and 5,865 normal controls. In the published literature, global verbal memory (e.g. total words recalled, learning across trials), non-verbal memory, trails B, and word fluency tests yielded the highest proportion of significant test score differences between schizophrenic patients and controls, although no test

completely separated the groups. The intellectual differences between the groups were said to be reliable and no significant correlations were observed between IQ effect sizes and moderator factors such as age, education, neuroleptic dose, gender, and age at onset.

The authors concluded that defective verbal memory is a reliable finding in the schizophrenia literature and it may be a circumscribed deficit in addition to a general deficit. They also suggested that the much reported deficit on the Wisconsin Card Sort Test (WSCT), a test of executive function, might simply be due to general intellectual impairment. The largest IQ differences between the groups were found when the WAIS-R was used. They also found there to be a considerable degree of variability around the NART mean and questioned its reliability as an index of premorbid ability. Another important finding was that putative tests of general function would not appear to be interchangeable, (which has implications when comparing studies). Digit span showed a modest degree of discriminability between the groups. There were also large effect sizes for spatial abilities including block design. In terms of language abilities, expressive and receptive language tests appear to be fairly powerful and moderately reliable discriminators of schizophrenic patients from controls, and not correlated with demographic and clinical moderator variables. Word fluency was lower in those with higher chlorpromazine doses, suggesting perhaps a medication or a severity effect.

An interesting summary of the literature examined was that the samples were disproportionately male (82.4%), and tended to include patients with 'fairly chronic' courses of illness, most were hospitalised in their early 20's, 78% were medicated at the time of neuropsychological testing. Only 13/204 studies were of unmedicated patients.

5.1.2.1 Memory and schizophrenia

Aleman et al. (1999), conducted a meta-analysis of memory impairment in schizophrenia. They reported on 70 studies that reported measures of long term memory, including free recall, cued recall, and recognition of verbal and non-verbal material, and also tests of short term memory (digit span). They reported an overall stable and significant association between schizophrenia and memory impairment, and

that the magnitude of memory impairment was not affected by age, medication, duration of illness, patient status, severity of psychopathology, or positive symptoms. Negative symptoms showed a small but significant relationship with memory impairment. Recall memory was worse than recognition memory; the authors suggest this could reflect a retrieval deficit in addition to less effective consolidation of material. Recognition trials may also be just easier to perform than recall trials.

Elliot and Sahakian (1995), in their review of the evidence reported that the mnemonic deficits and deficits in executive processing may be circumscribed deficits in schizophrenia set against a background of general impairment and IQ decline (Nelson et al., 1990; Frith et al., 1991). Saykin et al. (1991, 1994) reviewed the literature and concluded that schizophrenia is associated with general impairment with selective impairment in learning and memory, and the authors implicated the temporal-hippocampal region, suggesting a loss of the normal connectivity between cortical regions.

Cutting (1985) in a major review concluded that although memory may remain intact in acute schizophrenics, memory impairments are common in chronic cases. McKenna et al. (1990) found memory disorder to be common and to be disproportionate to the general intellectual decline, and suggested that in some patients it is similar to an amnesic syndrome. They found relative sparing of short-term memory versus long-term memory and this was not due to a medication effect (Tamlyn et al., 1992). Specific deficits in episodic and semantic memory have been noted with relative sparing of procedural learning and implicit memory (Clare et al., 1993). Allen et al. (1993) suggested that the problem with semantic memory might be due to impairments in the processes that retrieve information from the stores and that these may differ among patients with differing symptoms. They suggested that patients with poverty of speech terminate their search of the lexicon prematurely while the patients with incoherence commit errors in selecting words for output. Paulsen et al. (1995) suggested that the memory difficulties shown in patients with schizophrenia are primarily caused by deficits in encoding and retrieval rather than storage, they also found impairment in speeded cognitive tasks with and without a motor component. The

deficit they noted on the Stroop was suggested to be one of slowed cognitive processing rather than a problem of interference. It has been suggested that recall impairments seen in mildly disturbed schizophrenics patients was related to poor encoding secondary to decreased organisational skills (Levin et al., 1989).

Executive function is a term which is generally used to describe the processes whereby cognitive systems are coordinated for the successful performance of complex tasks and is very important in the planning and execution of complex behaviours and in the generation of a strategic approach to complex problems in the monitoring of performance and in the revision of strategies and behaviours that cease to be appropriate (Elliott and Sahakian, 1995). Baddeley (1986, 1992) proposed that working memory is a general-purpose system involved in a wide range of cognitive operations requiring the simultaneous storage and processing of information, incorporating executive functions. Deficits have been seen on tests of executive function including on a computerised version (Owen et al., 1991) of the Tower of London task (Shallice, 1982) by Pantelis et al. (1991) (cited in Elliot et al., 1998), and the WCST (e.g. Weinberger et al., 1986; Weinberger, 1988). Elliot et al. (1998) found that patients even in the absence of general intellectual decline, showed a marked tendency to perseverate on a computerised set shifting task based on the WCST (Owen et al., 1993), suggesting it may be a selective deficit. The difficulties in assessing executive function include the problem that the tasks are by definition complex and depend on high degrees of subject compliance. (There is much individual variation between patients and this led Shallice et al. (1991) to implement a single case study approach arguing that the group mean of a heterogeneous group will poorly reflect the behaviour of any individual in the group). Glahn et al. (2000) attempted to disentangle abstraction and working memory so that the effects of each cognitive domain could be independently analysed. They found that group differences in WCST performance appear to be attributable to the patients' inability to maintain information over a short delay, before that information is used for more complex cognitive operations, suggesting a memory component to the deficit.

5.1.2.2 IQ in Schizophrenia

Aylward et al. (1984) conducted a meta analysis of studies of intelligence in schizophrenia. In summary the authors concluded that the findings suggest that schizophrenia is associated with intellectual deficits across the life span. They presented evidence that pre-schizophrenic children, adolescents, and young adults perform below matched controls on a variety of standard measures of intelligence. Also VIQ tended to be higher than PIQ (supported by Jones et al., 1994; Done et al., 1994). They reported that no more specificity in the pattern could be outlined. They also reported that IQ was related in many studies to indices of prognosis, particularly higher IQ lead to a better prognosis. They questioned the possible role of IQ as a manifestation of the predisposition to schizophrenia, or as an independent mediating factor in those predisposed. Also there appeared to be evidence for greater IQ deficits in males than females (e.g. Offord and Cross, 1971). Little evidence was found for decline prior to onset of symptoms.

David et al. (1997) did not find any indication that low IQ was related to age at onset for schizophrenia, in contrast to Bilder et al. (1992) who found that the patients with the earliest onset premorbid problems tended to have the poorest adult neuropsychological functioning. However, it must be recognised that the definition of 'onset' is not standardised. Increased risk for schizophrenia has been identified in subjects with learning difficulties (Doody et al., 1998; Sanderson et al., 1999) supporting the association between schizophrenia and intellectual impairment and possibly developmental brain dysfunction. Goldberg et al. (1990), in a study of twins, reported that the twin with schizophrenia was invariably more intellectually impaired than the unaffected twin. Kremen et al. (1998) studied 547 offspring from the National Collaborative Perinatal Project. They tested the hypothesis that low IQ, large IQ fluctuations regardless of direction, and large IQ declines would predict the presence of adult psychotic symptoms. The 10% of individuals with substantially larger than expected IQ declines from age 4 to 7 had a rate of psychotic but not other psychiatric symptoms at age 23 that was nearly 7 times as high as that for others. Decline in IQ appeared to be specific to psychotic symptoms but not to schizophrenia. Low IQ at age 7 predicted psychotic symptoms at 23 but the IQ decline was a better predictor. Decline

in IQ had a greater predictive power than parental socio economic status, they found that socio-economic status was associated with IQ decline but not with later psychotic symptoms. It appears that both low IQ and a decline in IQ may be independent risk factors for schizophrenia.

5.1.3. When do the deficits arise, and do they progress?

Deficits appear to be present in first onset cases. Some studies that have selected chronic patient groups for comparison with each other across age cohorts have found no evidence of cognitive decline (Goldberg et al., 1993; Hyde et al., 1994). While there is evidence of enduring memory deficit after psychotic episodes the state trait debate has not been resolved (Seidman et al., 1992). Saykin et al. (1994) investigated a group of 37 never medicated patients and 65 previously, but not currently, medicated patients with a mean duration of illness of 9 years. Compared to a healthy control group both patient groups displayed general deficits and selective deficits in learning and memory were identified (particularly story recall from the WMS, paired associate learning, and California Verbal Learning Test, total of trials I-V). Hoff et al. (1991) found no differences between first episode and chronic cases. The groups were followed up at two years (Hoff et al., 1992) and they showed improvement from baseline on measures of executive function and attention but memory impairment remained. At later follow-up (Hoff et al., 1999) there was no evidence of greater cognitive decline in the schizophrenics compared to the controls. Centis et al. (1997) reported on a group of 30 neuroleptic naive patients and 30 previously medicated patients, and found generalized deficits in all functional domains except motor skill and a greater level of impairment on verbal memory, but no deterioration at 19 months follow-up.

Mohamed et al. (1999) studied 94 first episode patients, including 73 neuroleptic naive patients, and 305 normal controls. They found that patients performed significantly worse than the comparison subjects on every neuropsychological variable except those assessing saving scores. 25/30 tests had effect sizes greater the 0.75 when the groups were compared. They found the greatest relative impairments on WAIS-R digit symbol (d= -0.52) and comprehension (d=-0.42) subtests. These authors suggested that the significant cognitive impairment across multiple ability domains is a core characteristic

of schizophrenia and is not caused by chronicity, treatment, or institutionalisation. Bilder et al. (1992) showed a decline in digit span performance and language, and improvement in attention, motor and general memory functions in 53 first episode cases at 18 month follow-up.

Cross sectional studies suggest that the neuropsychological profiles of patients remain stable (Goldberg et al., 1993) or declines over time (Sweeney et al., 1992). Chen et al. (1996) reported on a cross sectional study of 204 patients in Hong Kong, with differing duration of illness. They compared prefrontal neuropsychological function and other cognitive performance. The WCST and semantic fluency were impaired early in the illness and did not significantly deteriorate as illness duration increased. There was some evidence the cohorts may not be equitable. The few longitudinal studies have concluded that neuropsychological functions either, remain stable (Nopoulos et al., 1994), or improve (Sweeney et al., 1991), suggesting that the findings from cross sectional studies may represent cohort effects. Sweeney et al. (1991) found improvement at follow-up on tests of attention/executive function, motor functioning, judgement of line orientation and recognition memory on the Rey Auditory Verbal Learning Test, but no improvement on verbal learning, verbal fluency, digit span, or immediate or delayed visual memory on repeated assessment of chronic 1st episode patients. Hutton et al. (1998) suggested that executive dysfunction might progress, particularly in the chronic phase. Rosmark et al. (1999) found patients performance to be stable over time.

Nelson et al. (1990) found no correlation between age and intellectual decline suggesting that there is little progressive decline in cognitive functions. Goldstein et al. (1994) found that patients with schizophrenia with histories of early developmental problems especially males, were significantly impaired compared to those without such a history displaying deficits in VIQ, abstraction, sustained attention, verbal and non-verbal memory, and motor function.

David et al. (1997) investigated the premorbid IQ of a cohort of Swedish army conscripts. They found poor performance on tests of VIQ and Mechanical knowledge

to be independently predictive of later schizophrenia. Reduced VIQ was also a risk factor for the development of other psychoses. The authors found that the highest risk for schizophrenia was found in the lowest IQ band, but within IQ ranges, there were linear trends of increasing risk with decreasing IQ. Cannon et al. (1999) described an American cohort of 9,236 individuals, they reported that at 4 and 7 the odds of later developing schizophrenia was linearly inversely associated with IQ, with siblings also performing more poorly than the general population. Poor premorbid social functioning and low educational attainment were more common among the retrospective reports of schizophrenic patients (Foerster et al., 1991a and 1991b). Jones and Done (1997) reported on data from two large prospective British Cohorts, in summary, both motor and cognitive development during childhood were shown to differentiate children who later developed schizophrenia. Developmental milestones were delayed and psychomotor dysfunction continued throughout childhood, also children who later developed schizophrenia had lower IQ scores than others. Jones et al. (1994) found a linear trend in the association between low IQ and schizophrenia with a rate ratio of 4.0 between the lowest and highest tertiles. While Done et al. (1994) reported stable patterns of deficits across the testing periods of 8/9 IQ points. Cannon et al. (1999) in a Finnish cohort, found pre-schizophrenics were worse at sports and handicrafts and were more often absent from school and had poorer conduct in class compared to others.

In review of the evidence for deficits predating the onset of psychosis, Davies (1998) reported that studies using army IQ exams (Goldberg et al., 1993) showed a reduction in performance after the onset of the illness. In addition studies using the NART found cognitive abilities decline after the onset of illness (Frith et al., 1991; and Crawford et al. 1992). The general cognitive impairment has been shown to represent a decline from premorbid levels (Nelson et al., 1990). Russell et al. (1997) reported no decline in IQ from childhood levels in those who later developed schizophrenia, and suggested that there is stable non-progressive impairment in cognitive functioning present before onset. However this sample is likely to be unrepresentative of most patients with schizophrenia as it was conducted on those who had presented for a childhood assessment at a psychiatric clinic and it cannot be ruled out that such individuals may be

expressing early non-specific manifestations of later illness. There is evidence to believe that the decline may occur within the first 2 years of the onset of the illness and is likely to be complete within the first five years of illness (Frith et al., 1991; Dunkley and Rogers, 1994), supporting the view that schizophrenia may be a 'static encephalopathy' as opposed to a deteriorating dementing disorder (Mockler et al., 1997). An average discrepancy of 16 points between premorbid and current functioning was found in the Harrow sample (Frith et al., 1991), 85% of these subjects were unemployed, strongly suggesting deterioration in social performance (Johnstone, 1991).

In summary, widespread general intellectual impairment appears to be characteristic of many patients with schizophrenia. Both low IQ and IQ decline appear to be independent risk factors. Aspects of memory and executive functioning may be impaired selectively in addition to the general impairment, or even in its absence (Elliot et al., 1998). Deficits appear to be present at onset, maybe before, and do not appear to progress beyond the first 5 years of illness.

5.1.4. Through what mechanisms do these deficits arise?

The underlying mechanisms have been difficult to identify. A shift away from structural imaging to functional imaging has shed some light on these mechanisms, and a concentration on the deficits related to specific symptoms, rather than the diagnosis in general, has been called for (Frith, 1996).

Evidence seems to be pointing towards the theories that implicate dysfunction in connections between subcortical areas, including the limbic system and the frontal cortex, and which particularly stress that prefrontal brain function may be compromised in schizophrenia. It could, of course be the case that the failure to establish strong correlations between cognitive performance and psychotic symptoms may represent an absence of such a relationship. Robbins (1990) proposed the presence of a core deficit in the frontal lobe interacting with sub-cortical deficits. Frith (1992) suggested that schizophrenia might be caused by an alteration in the functioning of the cortico-striatal functional loop proposed by Robbins (1990). Jaskiw and Weinberger (1992) proposed a cortically based abnormality and dysfunction of cortico-limbic connectivity. These

theories allow for interactions between individual patient characteristics and the underlying pathology and so may be able to account for the broad individual variation observed among patients. Frith (1995) suggested that damage to the basal ganglia may be implicated in the findings of circumscribed deficits in motor slowness, medial temporal lobe structures may be implicated in memory deficits, and the prefrontal cortex may be implicated in the impairment of executive functioning. It has been pointed out that while prefrontal damage is a sufficient cause of executive dysfunction it is not a necessary one, it can also arise from damage in other areas (Goldberg and Bilder, 1987). Weinberger (1987) suggested that the frontal lobe dysfunctions might be relatively "silent" in childhood, as some pre-frontal structures are not yet fully developed. This would have implications for comparing cognitive evaluation between childhood and adulthood. Gur et al., (1997) suggested that schizophrenia should be thought of as a fronto-temporal disorder because of the finding of reciprocal inter-connectivity of prefrontal regions with the hippocampus (Goldman-Rakic et al., 1984) and the rest of the brain (Fuster, 1980; Nauta, 1971). In summary, some deficit or deficits in frontal-temporal connectivity are implicated in the pathophysiology of schizophrenia.

5.1.5. How do the deficits relate to symptoms?

There is some evidence that different symptoms are associated with different neuropsychological deficits. Negative features were associated with IQ decline whereas severity of positive symptoms was not associated with intellectual impairment or speech problems on standard psychometric tests (Frith et al., 1991). A framework to explain the different symptoms of schizophrenia was formulated by Frith (1987, 1992), and it was proposed that the central impairment in schizophrenia is in the initiation and monitoring of actions. There are two routes to actions, one, which is dependent on external factors, and one, which is driven by internal goals and willed intentions. Negative symptoms may reflect impairment in generating willed intentions such that actions are mainly reliant on the stimulus driven route. Positive symptoms may represent a failure of monitoring such that actions are not seen as the product of willed intentions. With deficits of self-monitoring, patients misattribute self-generated actions to an external agent (Frith, 1987) and this discrepancy then leads to delusions.

Furthermore, there would be different physiological systems underlying the different tasks, with stimulus driven actions involving the lateral systems and willed actions, the medial systems (Goldberg, 1985, quoted by Frith, 1992) involving the basal ganglia and dopamine systems. Frith described how deficits in willed actions could explain many of the negative features of schizophrenia, while deficits in self-monitoring could explain many of the positive features.

Saykin et al. (1991), found a strong correlation between negative symptoms and neuropsychological change between intake and follow-up. Silverstein et al. (1994) found no relationship between neuropsychological summary scores and BPRS symptoms. Morrison-Stewart et al. (1992) found tests of general performance to correlate with symptom scores suggesting severity to be an important factor influencing performance on neuropsychological tests. Probably key in this research is the extent to which deficits are state or trait related, as symptoms come and go.

Frith (1992) suggests that the focus of studies in schizophrenia should not be that schizophrenia is associated with certain cognitive abnormalities, but that certain symptoms are. Liddle (1987b) and Liddle and Morris (1991) found that patients with different signs and symptoms do show different patterns of performance on neuropsychological tests. Liddle (1987a) found three clusters of signs and symptoms to capture the current mental state of most patients including psychomotor poverty (poverty of speech, actions and thoughts) disorganisation (incongruity of affect and incoherence of speech), reality distortion (hallucinations and delusions). The three clusters were found to be associated with different patterns of test performance. More negative type symptoms were associated with general cognitive impairment but the features of reality distortion were not (Frith et al., 1991). It is highly likely that over the course of the illness the patients' symptoms may change, with likely all patients having displaying symptoms of reality distortion at some time point.

Zalewski et al. (1998) conducted a review of the neuropsychological differences between paranoid and non-paranoid patients. They reviewed 32 studies related to intellectual functioning, attention, memory, language, and visual-spatial and motor

functions. There was little support for neuropsychological differences between the subtypes. Mahurin et al. (1998) found support for greater cognitive impairment associated with negative symptoms than positive symptoms (Strauss, 1993, Buchanan et al., 1994). Nelson et al. (1990) found that patients' slower motor speed and cognitive speed was correlated with the presence of negative symptoms.

No direct association was found between negative and positive systems and attentional dysfunction as measured by the CPT-IP (Cornblatt et al., 1997) a group of 58 patients.

In summary, there is some evidence that different symptoms relate to different deficits as measured by neuropsychological tests. How the observed neuropsychological deficits relate to symptoms has not frequently been investigated, and needs further work. It is likely that the combined work of the fields of cognitive neuropsychology and functional imaging will yield clearer answers in the future.

5.1.6. The Continuous Performance Test

In 1994 Cornblatt and Keilp reviewed over 40 studies that used various versions of the CPT as the primary measure of attention. They found that studies of normal subjects, affected patients and various at risk populations demonstrated that the CPT is a psychometrically sound procedure that consistently discriminates affected patients from controls. They reported that the more difficult versions of the CPT, which place high demands on information processing and often involve various types of distraction, have shown that impaired attention is evident in patients regardless of clinical state, is detectable before illness onset, apparently heritable, specific in terms of distinct profile patterns to schizophrenia, and is predictive of later behavioural disturbances in susceptible individuals. They were concerned with whether attention, as measured by the CPT various forms could be a valid phenotypic indicator of the schizophrenia genotype (a stable deficit/trait intermediate between genotype and clinical phenotype). Typically schizophrenia patients and subjects in populations at risk for schizophrenia are characterised by lower CPT, d' values (a measure of the subjects ability to discriminate a signal from background noise). CPTs have been historically considered as vigilance tasks. Medication may enhance performance but does not appear to elevate

it to normal levels. The classic versions are sufficient to distinguish patients and controls but more challenging tasks are necessary to distinguish HR populations from controls (e.g. Rutschmann et al., 1986). Cornblatt and Keilp (1994) reported that the more difficult variants of the CPT paradigm have been consistently effective in HR investigation (e.g. Nuechterlein 1983). Mirsky et al. (1992) administered 4 CPT tasks of varying difficulty level to two independent family samples and found that patients were significantly impaired versus controls on all tasks, while relatives were similar to controls on 3 tasks and only approached patient performance levels on the auditory CPT task. Studies using the relatively challenging CPT-IP (Cornblatt et al., 1988) have demonstrated attention deficits in the unaffected offspring of parents with schizophrenia (Cornblatt et al., 1989, 1992), in unaffected adult siblings (Franke et al., 1994), and in psychometrically defined schizotypal subjects (e.g. Lenzenweger et al., 1991), although the association between schizotypy and CPT deficits has not always been reported (Laurent et al., 1999; Franke et al., 1994). Performance on the CPT-IP appears to be heritable in normal families (Cornblatt et al., 1988) and taps a spatial and verbal component, and verbal and spatial items are of comparable difficulty. It was reported that relatives performed significantly worse than controls on d' for the shapes condition, and for all d' values the pattern was for higher scores for controls, followed by relatives, and poorest for patients with patients making more random errors in the standard and slow numbers conditions (Laurent et al., 1999). Franke et al., (1994) found that both patients and siblings were worse than controls on the CPT-IP and only the patient's performance deteriorated in the presence of distraction. Significant deficits were found in a high-risk group on tests that required sustained attention and information processing under high perceptual loads, with deficits being particularly prominent for the processing of visual stimuli (Schreiber et al., 1992). In the Roscommon family study Mirsky et al. (1995) found that a substantial attentional deficit characterised the patients with schizophrenia and also their sibling with a DSM III-R diagnosis but not the well siblings. Steinhauer et al. (1991) found that d' scores on a degraded visual version of the CPT were lower in the brothers of schizophrenic patients, who had a diagnosis of schizophrenia spectrum disorder, than in those with other diagnoses.

CPT-IP deficits have been seen in subjects with affective disorders, and in the offspring in such patients, but these deficits were different to the deficits found in schizophrenia and HR for schizophrenia, samples (Cornblatt et al., 1989). Deficits in CPT performance among the offspring of patients with an affective psychosis, were not directly related to later behavioural disturbance whereas they were in the offspring of patients with schizophrenia in the New York High Risk Study (Cornblatt and Erlenmeyer-Kimling, 1985; Cornblatt et al., 1989, 1992; Winters et al., 1981). Cornblatt et al. (1992) have linked childhood attentional problems to social deficits in adulthood particularly social isolation. Erlenmeyer-Kimling and Cornblatt (1987) reported lower signal/noise disturbance on a memory load CPT at age 7-12 among the HR children who were hospitalised or in psychiatric treatment in late adolescence. The subgroup of children of schizophrenic parents who showed psychopathology in late adolescence was the source of CPT deficits at age 7-12.

In a study by Buchsbaum et al. (1990) of PET scans using a challenging version of the CPT in patients and controls, decreased metabolic activity was observed in the prefrontal cortex and also a reduction of normal lateralized activity in temporo-parietal regions was noted in patients and the authors suggested that it may be caused by metabolic dysfunctions within subcortical regions, and basal ganglia, implicating dopamine neural transmission. Keilp et al. (1997) investigated brain functioning during the performance of the numbers and shapes subtasks of the CPT-IP. The results indicated that the two tasks produced different patterns of functioning within 2 general areas of the brain. During the numbers task, left sided activity was increased on multiple transverse slices in an anterior subcortical region that incorporated the anterior cingulate, frontal white matter and much of the basal ganglia. Left sided activity also increased in a posterior subcortical region including the left side of the thalamus. They found relative perfusion to occipital regions, bilaterally, which was more extensive during the shapes task.

Cornblatt et al. (1997) in a study of 58 patients tested on the CPT-IP at admission and at 4-6 week follow up, when ready for discharge, found that attention appeared to be independent of clinical features of schizophrenia, including age at onset of symptoms

and chronicity (supported by Winters et al., 1981; Finkelstein et al., 1997). The authors suggest that impaired attention reflects a biologically based abnormality that is independent of clinical symptoms prior to the onset of the illness.

The majority of studies have found that a decline in attention over time is not the critical impairment in schizophrenia, but that deficient processing capacity is the overriding deficit (for reviews, Nuechterlein and Dawson, 1984 Cornblatt and Erlenmeyer-Kimling, 1985), which is likely to be more sensory or perceptual in nature (Nuechterlein and Dawson, 1984).

In summary, deficits on the CPT, particularly lower d' values, have been purported to be a risk indicator for schizophrenia.

5.1.7. Medication effects

The extent to which medication affects patient performance on neuropsychological tests is not clear. The majority of studies have been conducted on medicated patients (Heinrichs and Zakzanis, 1998). Neuropsychological research on neuroleptic naïve subjects is a noble goal, however, it is frequently impossible given the florid states of many of these patients when they first present for treatment. The gap between performance and ability is likely to be particularly marked in very ill patients. There is little consensus regarding the best time to begin testing patients and there is much individual variability in the profile of illness progression. Also, the non-medicated patients you can test may be very atypical.

Attentional dysfunction on the CPT-IP did not appear to respond to standard neuroleptic medication (Epstein et al., 1996), and did not appear to improve with improvement in symptoms (Finkelstein et al., 1997). It has been shown that anticholinergics and minor tranquillisers can cause memory impairment (Frith, 1984). It has been reported that no consistent or reliable observations concerning medication status in relation to IQ and schizophrenia could be determined (Alyward et al., 1984; Heinrichs and Zakzanis, 1998). Nopoulos et al. (1994) found 35 first episode patients not to improve on tests of memory (verbal and non-verbal learning and memory), tasks of complex attention and

set shifting tasks improved with treatment. Shedlack et al. (1997) found a medication effect on the immediate condition of a visual reproductions test, for the combination of anticholinergic and antipsychotic medications but illness duration was not associated with test performance.

The above section suggests that the effect of medication on neuropsychological assessments is not known, and medication is possibly a confounder in research and may be a moderator factor for some aspects of function. Neuroleptic naïve patients are difficult to test and are rare in studies, especially in large numbers. It is unlikely the problem can be solved for patients, however for those HR subjects who are tested before and at onset it may be possible to illuminate the specific neuropsychological deficits before medication becomes a factor in the equation.

5.1.8. Neuropsychological investigations in HR and family studies

Findings with the CPT were reported earlier in section 5.1.6. Neuropsychological measures have been investigated extensively in HR groups. The high-risk studies attempted to identify markers to detect genetic risk. A risk indicator has been defined as a biological, cognitive, or psychological characteristic that may reflect liability to developing schizophrenia (Kremen et al., 1992). Garver (1987) outlined the criteria for a genetic marker of biological risk including; - the marker must have a different distribution in psychotic and control populations, - the marker must be a stable trait, - it must be more frequent in family members than in the general population and associated with spectrum disorders in family members, -deviation must occur at higher frequency in offspring before the development of psychotic spectrum disease onset, -deviation in the offspring will be associated with later development of psychotic spectrum disease, - marker identification is non invasive and must be able to be used with high reliability.

5.1.8.1. IQ in high-risk subjects

An effect size of 0.39 was reported across studies comparing IQ in the offspring of schizophrenic parents with the offspring of normal control parents (Alyward, 1984). The effect size was smaller when the pre schizophrenic individual was compared to siblings or peer controls. No significant differences were found when the HR offspring

of parents with schizophrenia were compared to offspring of those with affective disorders. Interactions between perinatal complications, socio economic status and high-risk status (off spring of schizophrenic or normal individuals) were observed in relation to deficits in IQ, with perinatal complications correlating with IQ deficits in the HR group and not the controls and SES correlated with IQ in normal subjects but not the HR group. Reductions in IQ scores have been reported in the offspring of subjects with other psychiatric disorders, but less markedly than in the offspring of patients with schizophrenia (Asarnow, 1988). The difficulty of how to handle IQ and social class in high-risk research has been debated, whether they should be considered as confounders, risk factors, or moderator factors, has been the topic of much discussion (Watt, 1984).

Kremen et al. (1994), reviewed the literature on potential neuropsychological risk indicators for schizophrenia from studies of the offspring of patients with schizophrenia and studies of adult relatives of patients with schizophrenia. They sought to answer two broad questions. Is there evidence of deficits? Are these deficits similar to those found in patients? They reported that the strongest evidence of impairment in relatives was in sustained attention, perceptual motor speed, and concept formation and abstraction and to a lesser degree, mental control encoding, primarily with distraction. They also reported that impairments of verbal memory and verbal fluency were found but have been less well studied in these groups and evidence of impairment in general verbal or visuo-spatial functioning has been largely negative. Findings were similar for children as for adult relatives. They commented that less is known about what deficits may differ between patients with schizophrenia and those with other psychiatric illnesses. The sensitivity and specificity of possible risk indicators is not known. Specificity for schizophrenia has been reported for reduced primacy (Harvey et al., 1981), impaired intentional learning with distraction (Driscoll, 1984), intrusion of distracters on dichotic listening tests (Spring, 1985), impaired ability to maintain grip tension (Rosen et al., 1991).

Summary of the neuropsychological findings in high-risk groups (Kremen et al. 1984).

5.1.8.2. Findings from the HR studies and studies of adult relatives of patients with schizophrenia.

The general finding from the HR studies have been reported in Chapter one, section 1.7. In terms of executive function and abstraction, there is evidence that children of parents with schizophrenia perform worse than children of normal controls on perceptual motor speed tests such as spokes, Stroop, visual search and cancellation and digit symbol/coding tests (the findings have been extensively reviewed by Erlenmeyer-Kimling et al., 1982, and Nuechterlein and Dawson, 1984). In other studies significant deficits were found in perceptual-motor speed tests among the adult relatives of schizophrenic individuals. Non-psychotic relatives were significantly slower on the Trail making test, particularly Trials B (Keefe et al., 1994, Pogue-Geile, 1990, Pogue-Geile et al., 1991, Pogue-Geile et al., 1992). Mirsky et al. (1992) found that adult relatives of schizophrenic patients were impaired on a composite measure comprising the Stroop, trail making, digit symbol and visual cancellation tests in an Irish and Israeli sample. Mirsky et al. (1995) reported that digit cancellation at age 11 but not age 17 predicted which of the HR group developed schizophrenia spectrum disorders at age 26 and 32 in the Israeli HR Study). The unaffected co-twins of affected monozygotic twins were not found to be significantly impaired on either the trails B (but they were on trials A) or the Stroop test (Goldberg et al., 1990). Tests of mental control/encoding (short term memory or selective attention tests) are also impaired among the relatives of schizophrenic individuals. It has been reported that children of schizophrenic parents had lower arithmetic subtests scores than controls (Landau et al., 1972; Mednick and Schulsinger, 1968; Sohlberg, 1985) but not observed by Worland and Hesslebrook (1980). Children of schizophrenic parents were not consistently impaired on digit span tasks (impairments observed by Cornblatt and Erlenmeyer-Kimling, 1984, 1985; not observed by Lifshitz et al., 1985; Mednick and Schulsinger, 1968; Worland and Hesslebrook, 1980) but did show deficits when these tasks included a distraction component (Harvey et al., 1981; Winters et al., 1981). They also performed poorly on the information overload test in which a matching task was performed with auditory

distraction (Cornblatt and Erlenmeyer-Kimling, 1985). Dichotic listening tests also showed mixed results (trend: Asarnow et al., 1978; negative: Hallett et al., 1986; Overschel et al., 1979). Mental control/encoding have also been studied among the adult relatives of schizophrenic individuals in the Israeli High-risk study. Adult children of schizophrenic parents had significantly worse digit span and arithmetic scores compared to controls (Mrisky, 1988). Goldberg et al. (1990) found no performance difference in these tasks between unaffected MZ co-twins of schizophrenic patients and controls. Asarnow et al. (1978) showed that the high-risk children performed more poorly on the object-sorting test, but this was not consistently found (Winters et al., 1981; Neale , 1982). In adults, parents and sibling of schizophrenic patients were found to be impaired on an object sorting task (McConaghy, 1959; Phillips et al, 1965) and on the WCST (Pogue-Geile, 1990; Pogue-Geile et al., 1991, 1992, Mirsky et al., 1992). Evidence of impaired WCST performance among adult relatives of schizophrenic patients was not always reported (Condray and Steinhauer, 1992, Roxborough et al., 1993 and Keefe et al., 1994, Goldberg et al., 1990). It was reported that siblings of schizophrenic patients had more WCST perseverative errors than controls (Franke et al., 1992). Both the Irish and Israeli sample of Mirsky showed perseverative errors (Mirsky et al., 1992). Also adult relatives were found to be impaired on the Luria-Nebraska relational concepts test (Condray and Steinhauer, 1992; Pogue-Geile et al., 1992).

Aside from vocabulary there has been little neuropsychological evaluation of verbal ability and language among HR children. Hallett and Green (1983) reported children were impaired on a speech sounds perception test. Most studies of adult relatives of schizophrenic individuals have not found differences in general verbal ability and 3 studies found significant impairments in verbal fluency tests (Keefe et al., 1994; Pogue-Geile et al., 1991; Roxborough et al., 1993). Goldberg et al. (1990) did not find verbal fluency deficits among the twin sample.

Studies of children of schizophrenic parents have not usually assessed verbal learning and memory. Rutschmann et al. (1980) found deficits on an auditory verbal recognition task, Roxborough et al. (1993) found significant verbal recall deficits among the adult

relatives of schizophrenic patients versus controls. Goldberg et al. (1990) found neither verbal recall nor verbal paired associate learning to be impaired in the unaffected twins but on they were impaired on the WMS.

General visual spatial ability and visual spatial learning and memory have not been studies much in HR samples. Many studies used embedded figures test in very young children but the results were inconsistent (Nuechterlein and Dawson, 1984). Goldberg et al. (1990) found no deficits in visual spatial ability as measured by the block design and road map tests, or visual recall on the WMS. Driscoll (1984) found no visual incidental learning impairments among children of schizophrenic parents with or without distraction, but showed deficits in intentional learning. Orvaschel et al. (1979) found no impairment among children of schizophrenic parents on a visual memory test. Impairments in motor function have been found consistently among the offspring of schizophrenic parents and have usually been evident as soft neurological signs such as disturbed gait, poor balance and coordination (Asarnow and Goldstein, 1986). Lifshitz et al. (1985) did not find deficits among children of schizophrenic parents on a tapping task, although they were significantly more impaired on mirror drawing tasks. Goldberg et al. (1990) did not find deficits on the go/no-go test in their unaffected co-twins. Rosen et al. (1991) found deficits in grip tension in relatives. Studies of the neuropsychological functioning among relatives of patients with schizophrenia point to deficits in sustained attention, perceptual motor speed, concept formation and abstraction and to a lesser extent, mental control-encoding. Other areas that have been less well researched and require additional research include verbal fluency and verbal learning and memory, although impaired language performance in the brothers of patients with schizophrenia has been reported (Condray et al., 1991). In terms of cerebral asymmetry in the offspring of parents with schizophrenia, story comprehension and recall lateralization effects were noted specifically, impaired binaural relative to monoaural (Hallett and Green, 1983; Hallett et al., 1986). Left ear advantage on a verbal dichotic listening task was reported (Hallett et al., 1986). Increased left handedness in a combined sample was noted (Hallett and Green 1983; Hallett et al., 1996). In adults, no handedness effects were noted (Kremen et al., 1992).

5.1.8.3. Further Studies of Adult Relatives of patients with schizophrenia

Conklin et al. (2000) found relatives to be impaired on the backward digit span task but not the forward digit span task. Shedlack et al. (1997) investigated language processing and memory in ill and well siblings from multiplex families affected with schizophrenia, compared to controls and found that sentence complexity was the only variable of a range of neuropsychological tests to distinguish siblings from controls. On CVLT, Lyons et al. (1995) found that relatives recalled significantly fewer words on both short and long delayed cued trials and had poorer recognition scores. The authors interpreted the relatives' difficulties with recall and discriminability as an indication of impairment of encoding rather than retrieval. Relatives used more serial than semantic clustering, suggesting a deficit in imposing an abstract organisational strategy on unstructured material, implicating executive deficits, suggesting dysfunction in the prefrontal- temporal limbic network (Levin et al., 1989; Seidman et al., 1992; Weinberger et al., 1992). Harris et al. (1996) examined aspects of attention and learning efficiency and memory in 28 parents of 14 schizophrenic patients where 8 of the families had a history of schizophrenia. They found significant differences between the proband and the parent in those with a negative family history but not a positive family history, on an aggregate index of attention. On an aggregate of learning efficiency, patients were generally worse than their parents. The authors concluded that a primary dysfunction in attention is the heritable component of schizophrenia. Sautter et al. (1995) found that familial schizophrenics versus non-familial schizophrenic had significantly more variable scores in areas of abstraction and problem solving and motor control. Accuracy of saccadic eye movements was found to be similarly impaired in both the patients and the relatives, and a greater VIQ –PIQ ratio was seen in the relatives and patients compared to controls, suggesting greater verbal than performance ability (Schreiber et al., 1992, 1995). Faraone et al. (1995) studied 35 nonpsychotic relatives of patients with schizophrenia and 72 normal controls using a clinical and experimental neuropsychological test battery. On the basis of adjusted composite scores (Chapman and Chapman, 1989) they found two neuropsychological functions to meet criteria for risk indicators of schizophrenia including verbal memory, and auditory attention (the scores were adjusted for age, gender and education/IQ). The

findings were not attributable to parental socio-economic status, education, or general visual-spatial ability or psychopathology. They found relatives to perform more poorly and to show greater variability than controls on the three functions of abstraction, verbal memory, and auditory attention. They had lower mean scores on verbal ability and mental control/encoding but not greater variability, and showed greater variability but no difference in mean scores on learning and motor abilities. They found no group differences on visual-spatial ability, visual memory or perceptual-motor functions. Kremen et al. (1997) investigated gender differences in 54 relatives and 72 normal controls (the augmented sample of Faraone et al., 1995) for the presence of differences in abstraction/executive functioning, verbal memory, and auditory attention. They found significant group by sex interactions for verbal memory and motor function and trends towards significant interactions for auditory attention and mental control encoding. With the exception of motor function it was female relatives who accounted for most of the impairment. The authors provided a speculative explanation that women may have a higher threshold than men for developing schizophrenia, and if this is the case that female relatives might be able to withstand greater impairments than men before developing psychotic symptoms. The consequence of this prediction would be that a group of relatives would contain an over representation of both less impaired men and more impaired women. Psychopathology did not account for neuropsychological deficits among relatives. However in this group 60% of men and 56% of women had a diagnosis of psychopathology, including major affective disorder, schizotypal personality disorder and various others such as eating disorders. Toomey et al. (1998) confirmed the original findings of Faraone et al. (1995) in the augmented sample of Kremen et al. (1997). This sample was examined again after 4 years (Faraone et al., 1999) and the initial findings were confirmed. Deficits in spatial working memory among adult relatives of patients with schizophrenia were reported (Park et al., 1995).

5.1.9. Methodological considerations

The degree to which differences in task complexity between tests influences the findings is not known. There is a difficulty with matching of experimental groups on

variables likely affected by the disease process, such as educational attainment, or current intellectual functioning (O'Carroll et al., 1992).

Controlling for confounders has not been a priority. Heinrichs and Zakzanis (1998) noted that moderator variables (e.g. medication, age at onset etc.) are not consistently reported in studies.

There is a degree of arbitrariness in relegating certain tests to putative domains of function (Lezak, 1995) and many tests are likely influenced by several component processes. Also differences in difficulty level between tests purported to examine the same domain of function they may lead to differences between groups in one study but not in another. For example if one study used the WSCT and another, a short computerised version of the Stroop as measures of executive function, it is likely that group differences may appear in 'executive function' in the first sample but not in the second. There is also a difficulty in looking at composite scores, as many tests of memory may tap different underlying processes and abilities.

There are many theoretical issues involved in the measurement of differential deficits. Chapman and Chapman (1978) wrote an article describing the measurement of differential deficit. They pointed out the numerous difficulties associated with identifying differential deficits, among them the different levels of task difficulties and differences in reliability of tests. They suggest that some conflicting findings regarding differential deficits in the schizophrenia literature may well be due to an artefact of the psychometric properties of the tests. The inability to remove the possible confounding factor of the differential discriminating power of the various tasks, limits the interpretability of many investigations.

5.1.10. Summary of the evidence for neuropsychological impairment

In summary neuropsychological impairments have been widely reported in patients with schizophrenia. A general cognitive impairment has been reported, with some evidence for circumscribed deficits in memory and executive functioning. As reported by Kremen et al. (1994) in their review, HR and family studies point to deficits in

sustained attention, perceptual motor speed, concept formation and abstraction, and to a lesser degree mental control/encoding. Deficits in verbal memory and verbal fluency were found to be present but have been less well studied in these groups. Differences in visuo-spatial ability, visuo-spatial learning and memory have not been well studied in these groups.

5.2. Neuropsychological functioning in subjects from the Edinburgh High Risk for Schizophrenia Study: baseline assessment

The samples involved and the tests administered were outlined in detail in chapters two and three respectively.

-From the literature summary presented here and in chapter one we could predict that on average the first episode patient group will show deficits on neuropsychological assessment in all domains of function, indicating the presence of a broadly based cognitive deficit. In addition they may show specific and possibly marked deficits in tests of executive function, attention as measured by the CPT-IP, and aspects of memory. Differences between estimates of current and pre-morbid intellectual function would also be expected, indicating a decline in performance from pre-morbid levels.

-Given the domains of function tested in this study, and given the results of other HR studies and studies of adult relatives of patients with schizophrenia, we would expect to see deficits in sustained attention (CPT-IP) and specifically reduced D prime values on the CPT-IP. Deficits would also be expected on tests of perceptual motor speed, and to a lesser degree, on tests of mental control/encoding. There may also be deficits in verbal memory and verbal fluency as the evidence for these functions are less robust. There is little evidence for deficits in visuo-spatial functioning and for general verbal deficits, but perhaps because these have been less well studied, so analysis of tests of these functions will be regarded as exploratory in nature.

-Generally it is expected that even in the absence of significant findings the results will show a trend for controls to perform better than the high-risk group who will perform

better than the first episode patient group. It is expected that the high-risk group will on average, but to a lesser degree, show similar patterns of deficits to the patients.

5.3. Statistical Analyses

Statistical analyses were conducted in SPSS version 8.0 (SPSS, 1997). Univariate analyses of variance were conducted, with group (high-risk, control, and patient) and gender as factors in the analysis, controlling for group by gender interactions. For data that were not normally distributed, non-parametric Kruskal-Wallis one-way analysis of variance was conducted to search for differences between the groups. A non-parametric method of assessing post hoc differences between the groups was used in order to further investigate significant Kruskal-Wallis values (Seigel and Castellan, 1988, 213-215).

The neuropsychological assessments were divided into areas of function as outlined in chapter 3, Table 3.1 and tested the areas of current intellectual function, premorbid intellectual function, executive function, perceptual motor speed, mental control/ encoding, verbal ability and language, and learning and memory.

The results from the initial baseline univariate analysis are presented in Table 5.1. F and P values are given for the main effects of group and gender and for the group by gender interactions. Post hoc Scheffe tests were calculated and the results are presented in the final column of Table 5.1. Significant differences were defined in all cases as p values of 0.05 or less. The post hoc Scheffe test was based on the marginal means and the results are presented without adjustment of multiple comparisons.

5.4. Baseline unadjusted analysis

5.4.1. Current Intellectual Function

On measures assessing current intellectual function (VIQ, PIQ, FSIQ, Block Design) controls performed significantly better than either the high-risk or patient group. The high-risk subjects performed significantly better than the patients in terms of VIQ, PIQ and FSIQ. There were no group by gender interactions for any of these measures.

Block design was investigated separately as it was employed in follow-up assessments as a measure of general ability, it is also a test of visuo-spatial ability. All scores were in the direction of controls achieving the highest mean scores, followed by the high-risk subjects and the patients performing most poorly.

5.4.2. Pre-morbid Intellectual Function

The three groups differed significantly in terms of pre-morbid intellectual function as measured by the National Adult Reading Test (NART; Nelson, 1982). Controls had significantly higher mean NART scores than the high-risk group who in turn had significantly higher scores than the patient group. Analysis of the spot the word test, which is similar to the NART, revealed both patients and high-risk subjects to perform significantly more poorly on this test than controls, but did not differ significantly from each other. In terms of the Spot the Word test only a significant difference was noted between the control and the HR group, while the HR and patient group means were exactly the same, the variability was less in the HR group.

A comparison of current, and pre-morbid, intellectual function.

A comparison of current and premorbid measures revealed that patients had a significantly greater NART- WAIS-R FSIQ discrepancy scores than either the high-risk group or control group. The speed and capacity of language processing test (SCOLP), is purported to be a measure of the difference between current and premorbid intellectual function (Baddeley et al., 1992). It is calculated by subtracting scaled scores on the Speed of Comprehension Test (putative estimate of current functioning) from scaled scores on the Spot the Word test (estimate of pre-morbid intellectual function). A positive score on this measure is said to indicate a decline from premorbid functioning. The only significant group difference noted was between the high-risk group and the patient group (who had a positive score on this measure), with neither groups scores differing from the controls. There was no significant gender by group interactions.

Table 5.1 . Neuropsychological variables compared across groups, initial univariate analysis.

	CONTROL, n=34 Mean (sd)	HR, n=157 Mean (sd)	PATIENT, n=28 Mean (sd)	GROUP F	P	SEX F	P	SEX*GROUP F	P	Post hoc Scheffe
Current IQ										
Verbal IQ	102.85 (12.61)	96.62 (11.58)	90.15 (14.18)	8.71	0.000	4.94	0.03	0.57	0.56	C≠P; HR≠C; HR≠P
Performance IQ	107.68 (15.88)	99.81 (14.25)	90.48 (13.52)	10.59	0.000	2.63	0.11	1.01	0.36	C≠P; HR≠C; HR≠P
Block Design	13.12 (3.16)	10.97 (2.82)	10.44 (5.52)	8.37	0.000	2.71	0.10	1.93	0.15	C≠P; HR≠C; HR=P
FSIQ	105.47 (14.13)	97.77(12.84)	89.52 (13.97)	11.27	0.000	4.59	0.03	1.15	0.32	C≠P; HR≠C; HR≠P
Premorbid IQ										
NART	105.23 (8.36)	98.36 (9.87)	96.56 (9.35)	8.10	0.000	0.50	0.48	0.30	0.74	C≠P; HR≠C; HR≠P
Spot the Word	11.03 (2.25)	9.46 (2.44)	9.46 (2.91)	5.35	0.005	2.34	0.13	0.52	0.60	C=P; HR≠C; HR=P
NART-FSIQ	-0.23 (11.14)	0.04 (12.11)	5.87 (8.40)	3.81	0.024	10.93	0.001	1.06	0.35	C≠P; HR=C; HR≠P
SCOLP	-1.35 (3.59)	-1.46 (2.96)	0.58 (3.21)	3.67	0.027	8.40	0.004	1.29	0.28	C=P; HR=C; HR≠P
Executive function										
STROOP 3	21.31 (5.09)	23.61 (5.54)	25.90 (5.01)	5.06	0.007	0.40	0.53	0.31	0.74	C≠P; HR=C(0.06); HR=P
STROOP 1-3	11.07 (4.96)	13.54 (5.37)	15.57 (4.51)	5.32	0.006	0.009	0.92	0.24	0.79	C≠P; HR=C; HR=P
FAS	40.53 (9.63)	37.95 (12.01)	28.09 (8.32)	9.44	0.000	1.09	0.30	0.25	0.78	C≠P; HR=C; HR≠P
Animals	17.97 (6.31)	15.57 (4.58)	12.26 (3.84)	10.24	0.000	6.71	0.01	0.84	0.43	C≠P; HR≠C; HR≠P
Ln Hayling timeA	14.36 (12.39, 16.79)	17.93 (16.69, 19.52)	22.80 (18.95, 28.41)	7.12	0.001	0.19	0.67	1.07	0.34	C≠P; HR≠C; HR=P
Ln Hayling timeB	27.66 (22.52, 34.09)	31.68 (28.79, 35.44)	40.70 (31.14, 52.61)	2.52	0.082	0.09	0.76	0.42	0.66	C=P; HR=C; HR≠P
Hayling time B-A	21.63 (28.18)	19.55 (26.57)	21.40 (20.80)	0.10	0.90	0.31	0.57	1.46	0.23	ND
*Hayling Total error	3 (0.75, 5.25)	4 (1, 14)	4.5 (1, 15)	2.07	0.36					ND
*Type A errors	3 (0, 3)	3 (0, 6)	1.5 (0, 6)	0.56	0.75					ND
*Type B errors	1 (0, 2.25)	2 (1, 4)	2 (1, 3)	7.69	0.02					C≠P; HR≠C; HR=P
Perceptual motor speed										
Digit Symbol	11.26 (2.71)	9.90 (2.69)	7.89 (2.59)	10.84	0.000	2.47	0.117	1.95	0.14	C≠P; HR≠C; HR≠P
Mental control /encoding										
Digits Forward	8.23 (2.26)	8.78 (5.89)	7.44 (2.13)	2.51	0.083	5.06	0.025	0.74	0.48	ND
Digits Backward	7.79 (2.31)	7.18 (2.30)	5.74 (2.36)	6.31	0.002	0.37	0.54	0.07	0.94	C≠P; HR=C; HR≠P
Arithmetic	10.21 (3.01)	9.34 (2.43)	7.96 (2.87)	6.71	0.001	11.21	0.001	2.62	0.07	C≠P; HR=C; HR≠P
Verbal ability and language										
Vocabulary	9.38 (1.87)	8.38 (2.13)	7.56 (2.31)	5.45	0.005	0.20	0.65	0.60	0.55	C≠P; HR≠C; HR=P

Table 5.1 cont.	**CONTROL N=34 Mean (sd)**	**HIGH RISK N=157 Mean (sd)**	**PATIENT N=28 Mean (sd)**	**GROUP**		**SEX**		**SEX*GROUP**		**Post hoc Scheffe**
				F	**P**	**F**	**P**	**F**	**P**	
*Token Test	163 (162, 163)	163 (161, 163)	160 (157.5, 162.5)	19.02	0.000					C≠P; HR≠C; HR≠P
Speed of Comprehension	12.37 (3.17)	10.93 (3.27)	9.46 (2.91)	8.61	0.000	1.86	0.17	0.44	0.64	C≠P; HR=C (0.08); HR≠P
Learning and memory										
RAVLT Trial 1	7.29 (1.93)	6.34 (1.85)	5.71 (2.27)	5.11	0.007	2.21	0.14	0.11	0.90	C≠P; HR≠C; HR=P
RAVLT Total 1-V	55.06 (8.58)	51.04 (8.56)	43.78 (10.48)	11.27	0.000	3.24	0.07	1.48	0.23	C≠P; HR≠C; HR≠P
RAVLT Delayed recall	13 (10, 14)	11 (9, 13)	7.5 (6, 10)	30.20	0.000					C≠P; HR≠C; HR≠P
RAVLT Recall B	6.41 (1.67)	6.03 (1.85)	4.43 (1.64)	11.33	0.000	0.47	0.49	0.80	0.45	C≠P; HR=C; HR≠P
RAVLT difference between I and V	6.00 (1.87)	6.01 (2.28)	4.89 (2.35)	2.82	0.06	0.25	0.62	0.35	0.71	C=P; HR=C; HR≠P
Recognition List A	13.26 (0.38)	12.99 (0.18)	10.69 (0.43)	13.05	0.00	2.07	0.15	0.10	0.91	C≠P; HR=C; HR≠P
Recognition List B	7.06 (0.47)	6.71 (0.23)	3.98 (0.53)	12.10	0.00	0.32	0.57	1.11	0.33	C≠P; HR=C; HR≠P
Visual Reprod.1 Immediate recall	37.88 (36.85, 38.84)	35.84 (35.28,36.38)	34.58 (33.10,35.89)	8.11	0.000	0.75	0.39	0.60	0.55	C=P; HR=C(0.08); HR=P
Visual Reprod.2 Delayed recall	36.22 (34.92,37.39)	33.93 (33.20, 34.61)	31.40 (29.13,33.22)	8.80	0.000	1.03	0.31	1.47	0.23	C≠P; HR≠C; HR≠P
Visual Reprod. Immed-delayed	2.72 (2.65)	2.64 (3.69)	4.18 (4.22)	1.58	0.21	0.91	0.34	0.37	0.69	ND
RBMT story Immediate recall	10.91 (3.81)	8.91 (3.29)	6.95 (3.09)	10.29	0.000	3.53	0.06	0.10	0.90	C≠P; HR≠C; HR≠P
RBMT story Delayed recall	10.04 (3.26)	7.78 (3.20)	6.14 (3.09)	11.24	0.000	1.64	0.20	0.04	0.96	C≠P; HR≠C; HR=P
STORY IMM-DEL	0.87 (1.59)	1.14 (1.58)	0.82 (1.52)	0.90	0.41	1.89	0.17	0.09	0.91	ND
*RBMT standardised score	22 (21.75, 24)	22 (20, 24)	20.5 (17, 23.25)	19.02	0.000					C≠P; HR≠C; HR≠P

* Non-parametric one-way analysis of variance (Kruskall-Wallis) was conducted, as the data were not normally distributed. This means that the gender effect couldn't be measured in the analyses but gender differences were not evident for these measures when investigated.

5.4.3. Executive Function

Stroop

On the Stroop test, the incongruous condition, and the difference between baseline and incongruous conditions, the controls performed significantly better than the patients, having faster times on Stroop 3, the incongruous condition, and less discrepancy between condition 1 (baseline) and condition 3 (incongruous test condition). There was a trend for controls to do better than the high-risk group on the Stroop variables. All differences were in the predicted direction of controls > high-risk > patients.

Verbal Fluency

Controls produced significantly more words on the summed 'F' 'A' 'S' trials than the patients and more but not significantly more than the high-risk group. All groups differed significantly in terms of the number of names of 4 legged animals produced, with controls producing more than the high-risk group and the high-risk group more than patients.

Hayling Sentence Completion Test

Time taken to complete section A of the Hayling Sentence Completion test was not normally distributed and was log transformed using the transformation log (log time A). The geometric mean and the 95% confidence intervals are presented in Table 5.1. Controls on average had significantly faster times in seconds on this measure than either the high-risk group or the patients, who did not significantly differ. Group differences were not found for the variable, Hayling B-A. This variable represents the time taken to complete section B of the task minus the time taken to complete section A. By creating this variable, the element of baseline speed of response is removed. In terms of overall Hayling error scores there were no differences across the groups. A Kruskal-Wallis one-way analysis of variance was used to investigate differences on this measure, as it was not normally distributed. When the errors were divided into type A errors (straightforward sentence completions, the most serious errors) and type B errors (words related to the sentence in some way), both the high-risk group and the patients were found to make significantly more type B errors than controls. The high-risk group made more type B errors than the other groups. The groups did not differ in terms of the number of type A errors made.

5.4.4. Perceptual Motor Speed

The digit symbol substitution test of the WAIS-R was the only measure of perceptual motor speed employed. The three groups differed significantly form each other on this measure. Again the controls had significantly higher mean age corrected scaled scores than the high-risk group or the patients.

5.4.5. Mental control/ encoding

Again sub-tests of the WAIS-R make up this domain of function. Raw scores for digits forwards and digits backwards were analysed separately due to the known differences in task demand. There were no significant group differences for digits forwards. Controls and high-risk subjects attained significantly higher scores than the patients on digits backwards. The same pattern was true for scores on the Arithmetic sub-test of the WAIS-R with controls and high-risk subjects scoring significantly better than patients.

5.4.6. Verbal ability and Language

On the age corrected scaled scores of the vocabulary sub-test of the WAIS-R controls performed significantly better than the high-risk group and the patients. The high-risk and patient groups did not differ on this measure. All groups differed significantly from each other on the token test. A non-parametric analysis was conducted for this measure. The medians are presented in Table 5.1. The controls had a higher mean rank than the high-risk group and the patient groups on this test. On the speed of comprehension test scaled scores, controls scored significantly better than the patient group and there was a trend towards higher scores in the controls than the high-risk group. The high-risk and the patients groups differed significantly from each other. There were no group by gender interactions noted for this domain of function.

5.4.7. Learning and Memory

5.4.7.1.Rey Auditory Verbal Learning Test

Many differences between the groups were found in this domain of function. On the initial recall trial of the Rey Auditory Verbal Learning Test (RAVLT), controls remembered significantly more words than either the high-risk group or the patient group; the latter groups did not differ. On the RAVLT total of trials one to five, all

groups differed significantly, with controls remembering significantly more words than the high-risk group and the patients. This remained true for the delayed recall trial of list A. On this measure (the analysis was conducted using non-parametric techniques as the measure was not normally distributed) patients performed significantly more poorly than either the controls or the high-risk group. The controls and the high-risk group did not differ on this measure. There was no significant difference between the groups in terms of number of words gained between trials one and five on the RAVLT (trial V – trial I). There was trend for patients to make fewer word gains than the high-risk subjects but not the controls. Patients had significantly poorer recognition of words from lists A and B compared to the other two groups. The average difference between the number of words from list A recognised from a series of 50 words and those remembered on the delayed recall trial for the high-risk group was 2.53 (s.e. 0.17), for the controls was 1.61 (s.e. 0.37) and for the patients, 2.66 (0.43). The HR and controls differed significantly from each other, and there was a trend for the control group and the patient group to differ (p=0.07). This variable gives an estimate of the difference between free recall and cued recall.

5.4.7.2.WMS-R Visual Reproductions

In Table 5.1 Visual Reprod1 and Visual Reprod2 refer to the immediate and delayed recall trials of the visual reproductions subtest of the Wechsler Memory Scale-Revised. The means presented in the Table are those transformed back from the normalised scale (X^4), confidence intervals computed on the normalised scale and transformed to the original scale are presented also. In terms of immediate recall, controls had significantly higher mean scores than the high-risk group and the patients, the patients and the high-risk did not significantly differ from each other. On the delayed recall section of the visual reproductions controls achieved significantly higher scores than the high-risk group and the patients. There was no significant difference in loss of information over time between the groups, as evaluated by analysing the differences between the immediate and delayed recall conditions of the visual reproductions task. All groups differed on the immediate recall of the story, on the Rivermead Behavioural Memory Test (RBMT), with controls remembering more than the high-risk group who remembered more than the patients. On the delayed story recall controls performed better than either the high-risk group or the patient group. The high-risk and patient

groups did not differ from each other. There was no significant difference in loss of information over time between the groups, as evaluated by analysing the differences between immediate and delayed recall story conditions.

5.4.7.3.Rivermead Behavioural Memory Test

All groups performed significantly differently from each other in terms of the total RBMT standardised scores. A non-parametric analysis was performed on the data. Controls did better than the high-risk group who in turn remembered more than the patient group. The medians, with 25^{th} and 75^{th} percentiles are given in Table 5.1.

5.4.8.Continuous Performance Test; initial analysis

The continuous performance test was analysed according to the methods suggested by Cornblatt et al. (1988). This analysis involved the three measures, described in detail in Chapter 3, including a measure of random errors (transformed to the log scale) and two signal detection measures, D prime and Log Beta. D prime is a measure of decline in sensitivity and log beta is a measure of shifts in response style or a tendency to over respond versus under respond. The recommended method of statistical analysis is to conduct a repeated measures analysis of variance to investigate the effect of both stimulus type (numbers and shapes) and distraction (absent or present) and the effect of speed (fast or slow). In order to evaluate whether there was a deficit in sustained attention and to look for evidence of abnormal distractibility, a 3 group (high-risk, control, and patient) by 2 stimulus (numbers and shapes) by 2 distraction (present or absent) repeated measures analysis of variance was conducted separately for log random, d'prime, and log beta measures. The results of this analysis are presented in Table 5.2 and are explained in the following section.

In order to investigate whether there was a deficit in speed of processing a 3 group (high-risk, control, and patient) by 2 stimulus (numbers and shapes) by 2 speed (slow or fast) repeated measures analysis of variance was conducted separately for log randoms, d'prime, and log beta measures. The results are presented in Table 5.3 and are outlined in the following section.

Table 5.2 CPT-IP distraction and stimulus conditions; unadjusted marginal means presented.

		High Risk N=126	Control N=30	Patient N=15	Group		Stimulus		Distraction		Stimulus * Distraction	
					F	P	F	P	F	P	F	P
Log Randoms												
Fast Numbers	No distraction	0.46 (0.62)	0.25 (0.52)	0.56 (0.61)								
	Distraction	0.64 (0.62)	0.46 (0.63)	1.03 (0.89)	3.15	0.04[a]	0.30	0.58	18.15	0.00	3.77	0.05
Fast Shapes	No distraction	0.56 (0.66)	0.40 (0.55)	0.66 (0.84)								
	Distraction	0.60 (0.73)	0.39 (0.56)	0.94 (0.74)								
D Prime												
Fast Numbers	No distraction	1.76 (0.83)	1.93 (0.89)	1.22 (0.58)								
	Distraction	1.64 (0.86)	1.67 (0.85)	0.99 (0.68)	8.00	0.00[b]	4.03	0.05	0.002	0.96	24.61	0.00
Fast Shapes	No distraction	1.69 (0.71)	1.95 (0.62)	1.15 (0.30)								
	Distraction	1.90 (0.89)	2.28 (0.86)	1.22 (0.56)								
Log Beta												
Fast Numbers	No distraction	-0.12 (0.74)	-0.06 (0.53)	0.04 (0.39)								
	Distraction	-0.32 (0.68)	-0.37 (0.75)	-0.27 (0.82)	1.23	0.60	0.59	0.44	3.88	0.05	8.79	0.003
Fast Shapes	No distraction	-0.19 (0.82)	-0.18 (0.96)	-0.06 (0.45)								
	Distraction	-0.24 (0.79)	-0.13 (0.62)	0.02 (0.46)								

None of the following interactions were significant, Stimulus * group; Distraction* group; Stimulus* distraction*group, and were not presented in the Table for ease of reading.

There were no gender differences, so it was not included in the model.

Post Hoc Scheffe test: [a] C≠P, HR=C (0.09), HR=P; [b] C≠P, HR=C, HR≠P

Table 5.3. CPT-IP speed and stimulus conditions; unadjusted marginal means presented

		High Risk N=126	Control N=30	Patient N=15	Group F	Group P	Stimulus F	Stimulus P	Speed F	Speed P
Log Randoms	Fast	0.46 (0.62)	0.25 (0.52)	0.56 (0.61)						
Numbers	Slow	0.35 (0.55)	0.22 (0.50)	0.98 (0.96)	4.58	0.01[&]	6.69	0.01	3.85	0.05
	Fast	0.56 (0.66)	0.40 (0.55)	0.66 (0.84)						
Shapes	Slow	0.48 (0.72)	0.34 (0.55)	1.06 (0.88)						
D Prime	Fast	1.76 (0.83)	1.93 (0.89)	1.22 (0.58)						
Numbers	Slow	2.24 (0.96)	2.33 (1.10)	1.36 (0.86)	8.38	0.00[£]	0.65	0.42	69.45	0.00
	Fast	1.69 (0.71)	1.95 (0.62)	1.15 (0.30)						
Shapes	Slow	2.28 (0.94)	2.59 (0.80)	1.61 (0.80)						
Log Beta	Fast	-0.32 (0.68)	-0.37 (0.75)	-0.27 (0.82)						
Numbers	Slow	-0.26 (0.87)	-0.24 (0.76)	0.10 (0.71)	0.77	0.58[%]	0.34	0.56	0.18	0.67
	Fast	-0.25 (0.79)	-0.13 (0.62)	0.02 (0.46)						
Shapes	Slow	-0.24 (0.94)	-0.27 (0.97)	-0.23 (0.82)						

The following interactions were controlled in the model; stimulus * group; speed* group; stimulus*speed* group, the results are not presented in the Table for ease of reading.

[&]C≠P, HR≠P. There was a speed by group interaction (Hotellings T, F=9.70; p=0.001).

[£] Post hoc Scheffe test revealed C≠P, HR≠P. There was a significant stimulus by speed interaction F=6.0, 0.01.

[%]There was a significant stimulus * speed interaction F=7.61, p=0.006.

5.4.8.1. Distraction conditions

Log Randoms

As outlined in Table 5.2, a significant group effect was observed for log randoms, with controls making significantly fewer random errors than the patient group. There was a trend for the high-risk subjects to make more random errors than controls, but there was no difference between the high-risk and patient groups for this measure. A significant effect of distraction was observed. A significant stimulus by distraction interaction was observed.

D Prime

For D'prime a significant effect of group was observed. The patient group had significantly lower d'prime scores than either the high-risk or control groups. There was a significant effect of stimulus. A significant stimulus by distraction interaction was evident.

Log Beta

There were no significant main effects for log Beta. There was a significant stimulus by distraction interaction.

5.4.8.2. Speed conditions

Log Randoms

As outlined in Table 5.3 a significant main effect of group was observed where patients had significantly higher log random scores than either the high-risk or control groups. Also a significant speed by group interaction was found for log randoms. This is visually displayed in Figures 5.1a for numbers and 5.1b for shapes. The patient group made more random errors in the slow conditions of both numbers and shapes compared to the fast conditions.

Fig 5.1a. Speed by group interaction ranks for CPT-IP numbers, log randoms

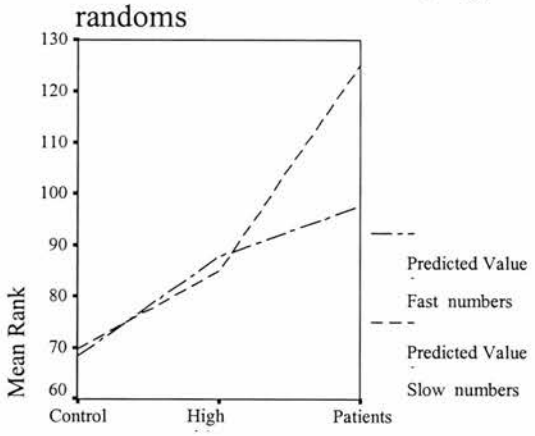
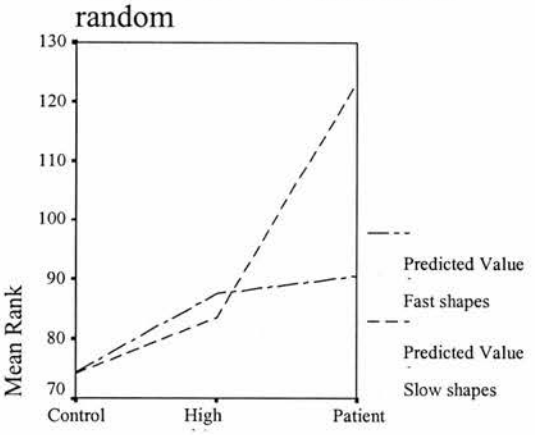


Fig. 5.1b. Speed by group interaction ranks for CPT-IP shapes, log random



Figures 5.1a and 5.1b CPT-IP group by speed interactions for log randoms (numbers and shapes) unadjusted analysis

D Prime

A significant group effect was observed for D'prime where a post hoc Scheffe test revealed that the patient group again had significantly lower scores than the high-risk group and the controls on this measure. There were no differences between the high-risk and control group. There was a large and significant main effect for speed but not for stimulus, and there were no significant interactions involving group.

Log Beta

There were no significant main effects for group, stimulus, speed, or any significant interactions involving group on this measure.

5.4.9. Summary of univariate unadjusted analyses

All groups differed significantly from each other in the predicted direction of Controls > HR >Patients on all measures of current intellectual functioning and on the NART an estimate of premorbid function. Evidence for executive dysfunction was found in the Patients compared to the Controls for the Stroop variables, verbal fluency measures, time to complete section A of the HSCT and the number of type B errors on the HSCT. The HR group performed significantly better than the Patients on verbal fluency, and were quicker to complete HSCT time B. Controls performed significantly better than the HR group on the verbal fluency measure 'Animals', time to complete the HSCT section A, number of type B errors on the HSCT, where the HR group were significantly worse than both other groups. All groups differed significantly, in the hypothesised direction on the measure of perceptual motor speed, digit symbol. In the domain of mental control/encoding, patients were significantly poorer than the other groups on digits backwards and arithmetic. For verbal ability and language tests, both the HR and Patient groups had significantly lower scores than controls on the vocabulary test, all groups differed in the predicted direction on the Token test, and speed of comprehension test (however there was only a trend between the HR and Control groups). On the SCOLP only the Patients and the HR groups differed. In the domain of Learning and memory significant differences between the three groups in the expected direction were found for the RAVLT total of trials 1-V, and delayed recall of List A, visual reproductions delayed recall, RBMT story immediate recall, and on the RBMT standardised score. Controls were significantly better than the HR and Patients for the RAVLT trial 1, visual reproductions immediate recall, and the RMBT story delayed recall, where the HR and Patients performances did not differ. The controls and the HR group performed significantly better than the patients on the RAVLT recall of list B. Compared to the Patients the HR group learned significantly more words across the RAVLT trials, neither group differed from the Controls.

Therefore deficits were found in all domains of function for patients relative to the HR and control groups. For the HR group relative to the controls, deficits were seen in all domains except mental control/encoding.

In terms of the CPT for the distraction conditions, both the controls and the HR groups performed significantly better than the patients in terms of log randoms, and d' scores (patients had lower d' scores). In the speed conditions, both controls and HR group made significantly less random errors than the patients, who were particularly impaired in the slow stimulus conditions, and had significantly higher d' values than patients. There were no differences between the groups in terms of log beta, for either the distraction or speed conditions. So patients made more random errors and had poorer sustained attention on the CPT-IP compared to the other groups.

5.5. Analysis of data from the neuropsychological assessment battery; Controlling for premorbid intellectual function (NART)

Due to differences between the groups both in terms of current and premorbid IQ, all variables were re-analysed with NART estimated pre-morbid IQ as a co-variate in the analysis. The issue of whether to control for intellectual function in this type of sample is well recognised. If the genetic deficit imparted is a global IQ deficit then controlling for it will have the effect of removing the differences of interest from the analysis, and control away the true effects. However such an analysis appeared appropriate, given the large effect of IQ on the other tests. For these reasons, it was decided that the analyses should be conducted both with and without controlling for IQ. The NART was chosen as the most appropriate estimate of IQ, in this sample, as it is an estimate of pre-morbid IQ, the subjects' highest intellectual function, and is least likely to be influenced by illness. Of course performance on the NART may be affected by the development of schizophrenia and so performance may not be an accurate reflection of ability in those who will develop the illness in time, however to control for NART appeared to be the best solution.

The WAIS-R subtests were included in this analysis, digits forwards, digits backwards, arithmetic, and digit symbol. Although digits forwards, backwards, and arithmetic sub-tests are known to have VIQ components it was thought necessary to control them for NART, given the capacities tested by these sub-tests. The vocabulary test was not analysed controlling for NART as it is highly correlated with overall intellectual function, particularly VIQ. The Spot the Word test and the SCOLP (a measure including the Spot the Word Test) were not analysed with NART as a covariate as the spot the word test is purported to be a similar measure to the NART.

Univariate analysis of co-variance models controlling for NART by group, and sex by group interactions were conducted. The models were evaluated according to standard statistical guidelines (Kleinbaum et al., 1998), and terms were eliminated from the model if not significant and if their removal improved the overall model fit. In the case of non-normally distributed data, a technique suggested by Conover and Inman (1982) was adopted. In this analysis both the dependent variable and the covariate were ranked and subject to a general linear model, parametric analysis of co-variance.

The results of the analysis are presented in Table 5.4.

5.5.1. Executive function

Controlling for NART FSIQ all but one group difference disappeared, given the large effect of NART FSIQ on most of the tests. On the Hayling Sentence Completion test the high-risk group made significantly more type B errors than the control group, but not the patients, and the patient group and the control group did not differ significantly from each other. Because the error scores on the Hayling are not normally distributed, a non-parametric analysis was employed and the ranks are presented in Table 5.4. The high-risk group had the highest error rankings for Hayling Sentence Completion Test total errors, and errors type B, compared to the other groups. However there were no significant differences between the groups in terms of type A errors and the high-risk group made significantly more type B errors than the controls who had the lowest ranking scores, but did not differ significantly from the patient group. The patients

received a ranking score intermediate between the other groups and did not significantly differ from either.

The error scores were not normally distributed and the converted error scores used in the analysis are weighted scores where extra scores are added the more errors that are made, so it is not simply an additive score. If subjects made 3 errors then the score was more than simply the addition of the scores for each of the 3 errors. In this sample 47% of the high-risk group, 53% of the controls, and 50% of the patients made no type A errors and 22% of the high-risk group, 49% of the controls and 22% of the patients made no type B errors. While all groups included similar numbers of persons making type A errors, almost 80% of both the high risk and patient groups compared to 50% of the controls, made more type B errors. The type B error scores made by the high-risk group achieved a higher rank than those for the patient group although the % of people making errors was the same, meaning that those who made errors, made more errors than the patients. Interestingly no main effect for NART was found for any of the Hayling measures, suggesting that this test does not rely heavily on intellectual ability for success. There were no significant interaction terms for any of the executive function tests. A main effect of NART was found for Stroop test measures and for verbal fluency measures.

5.5.2. Perceptual Motor Speed

There was a significant main effect for NART but no effect of group, gender, or any interactions on the digit symbol sub-test.

5.5.3. Mental Control Encoding

No group differences existed for digits forward, digits backward or arithmetic sub-test. There were significant main effects for NART on these three tests.

5.5.4. Verbal ability and Language

No significant group main effects were found for either the token test, or the Speed of Comprehension test. There were no significant interactions noted here.

5.5.5.Learning and Memory

There was no main effect for group for total on the RAVLT (sum of trials 1 to 5), the delayed recall trial, or the recall of list B trials. Similarly there were no main effects of group for the immediate and delayed recall section of the visual reproductions test or for the RBMT story immediate and story delayed trials. There were significant main effects for NART for all of these variables, however there were no significant interactions present. There was a significant group main effect for the first recall trial of the RAVLT, a measure of short term memory. This was accompanied by a NART by group interaction for this variable. In the high-risk group an increase in NART was accompanied by a smaller predicted increase in the number of words remembered on RAVLT trial one than for the other groups, suggesting less of a reliance on NART for success on this task in the high-risk group. The patients had significantly lower scores on the RAVLT recognition task for list B than the other groups. In addtion the patients had learned significantly less words across the trials than the other groups defined as the difference between RAVLT trial I and trial V. No differences were found for the amount of information loss between the RBMT story immediate and story delayed recall. A significant group effect was found for the RMBT standardised total score, where post hoc tests revealed that the controls scored significantly better that the HR or the patient group who did not differ from each other.

5.5.6. General Mental Ability

The block design test, a good measure of general mental ability, was analysed controlling for NART. The block design test is presented individually due to its importance in this study for the repeat assessments. When controlling for NART I.Q. a significant group main effect remained, where the high-risk group and the patients were significantly poorer than controls on this task. This main effect was accompanied by a significant interaction between NART and group. The controls had higher predicted block design scores, which appeared less variable than the patient or high-risk group. Block design scores appear less dependent upon NART scores in the control group than in the other groups. In the high-risk group increases in NART are accompanied by more dramatic increases in predicted block design scores than in the other groups. The presence of such an interaction poses a problem for the interpretation of the main effect

of group as the validity of the analyses of co-variance is based on the assumption of no such interaction.

Table 5.4 Neuropsychological variables compared across groups with NART estimated IQ as a co-variate.

	CONTROL N=34 Adjusted mean (standard error)	HIGH RISK N=150 Adjusted mean (standard error)	PATIENT N=25 Adjusted mean (standard error)	GROUP		SEX		NART		SEX*GROUP		NART*GROUP	
				F	P	F	P	F	P	F	P	F	P
Executive function													
STROOP3	23.11 (1.15)	23.45 (0.42)	25.17 (1.13)	0.19	0.82	0.002	0.96	15.98	0.000	0.89	0.41	0.27	0.76
STROOP 1-3	12.87 (1.13)	13.46 (0.42)	15.16 (1.12)	0.56	0.57	0.15	0.69	10.59	0.001	0.48	0.62	0.77	0.46
FAS	37.55 (2.14)	38.68 (0.83)	30.25 (2.47)	0.14	0.87	2.01	0.16	23.89	0.000	0.05	0.95	0.12	0.89
Animals	17.56 (0.97)	15.74 (0.37)	13.08 (1.09)	0.51	0.60	5.46	0.02	6.66	0.011	1.50	0.22	0.31	0.74
Ln Hayling time A	0.98 (0.03)	1.05 (0.01)	1.11 (0.03)	1.16	0.32	0.35	0.55	2.96	0.087	1.07	0.34	0.91	0.41
Ln Hayling time B	1.20 (0.40)	1.29 (0.01)	1.29 (0.04)	0.37	0.69	0.01	0.90	0.89	0.35	0.76	0.47	0.32	0.73
Hayling time B-A	22.83 (5.64)	19.53 (2.17)	20.99 (5.57)	0.05	0.95	0.27	0.61	0.23	0.63	1.36	0.26	0.04	0.96
Hayling total errors	96.19 (13.18)	109.66 (5.01)	94.39 (12.98)	0.13	0.88	5.01	0.03	1.02	0.31	2.38	0.09	0.11	0.90
Type A errors	110.51 (12.54)	108.44 (4.83)	97.93 (12.35)	0.33	0.72	3.72	0.05	2.02	0.14	1.60	0.20	0.74	0.48
Type B errors	83.87 (10.69)	113.75 (4.95)	102.09 (12.12)	3.30	**0.04***	1.50	0.22	0.55	0.46				
Perceptual motor speed													
Digit symbol	10.87 (0.53)	9.97 (0.20)	8.38 (0.54)	0.23	0.80	1.87	0.17	8.27	0.004	1.68	0.19	0.24	0.79
Mental control / encoding													
Digits forward	7.64 (0.40)	8.48 (0.15)	7.80 (0.40)	0.19	0.83	8.66	0.004	35.90	0.000	0.93	0.39	0.21	0.81
Digits backward	7.12 (0.45)	7.32 (0.17)	2.23 (0.45)	0.31	0.73	1.03	0.31	24.77	0.00	0.53	0.70	0.16	0.85
Arithmetic	9.17 (0.46)	9.45 (0.18)	8.63 (0.46)	1.21	0.30	19.22	0.00	53.08	0.00	2.91	0.06	0.97	0.38
Verbal ability and language													
Token test	114.59 (10.94)	107.57 (4.26)	80.50 (11.65)	2.03	0.13	0.52	0.47	13.86	0.000	0.99	0.37	0.41	0.66
Speed of comprehension	11.28 (0.58)	11.16 (0.23)	9.51 (0.57)	0.03	0.97	1.64	0.20	44.43	0.000	1.12	0.33	0.04	0.96
SCOLP	-1.22 (0.70)	-1.48 (0.26)	0.32 (0.65)	0.30	0.74	7.47	0.007	0.008	0.93	1.18	0.31	0.51	0.60
Learning and memory													
RAVLT Trial 1	6.60 (0.39)	6.35 (0.16)	6.06 (0.40)	3.06	**0.05#**	2.69	0.10	15.82	0.000	0.19	0.83	3.26	0.04
RAVLT Total I-V	52.55 (1.76)	51.19 (0.69)	45.56 (1.76)	0.22	0.81	2.82	0.09	12.39	0.001	1.20	0.30	0.40	0.67
RAVLT Delayed recall	130.96 (11.40) 13 (10, 14)^	108.73 (4.48) 11 (9, 13)^	64.35 (11.44) 7 (6, 10)^	1.42	0.24	5.44	0.02	4.15	0.04	0.34	0.71	0.27	0.76
RAVLT Recall B	6.13 (0.37)	6.05 (0.14)	4.45 (0.37)	0.26	0.77	1.06	0.30	8.06	0.005	0.64	0.53	0.05	0.95

Table 5.4 cont.	**CONTROL N=34 Adjusted mean (standard error)**	**HIGH RISK N=150 Adjusted mean (standard error)**	**PATIENT N=25 Adjusted mean (standard error)**	**GROUP**		**SEX**		**NART**		**SEX*GROUP**		**NART*GROUP**	
				F	**P**	**F**	**P**	**F**	**P**	**F**	**P**	**F**	**P**
RAVLT difference between I and V	6.61 (0.46)	6.05 (0.18)	4.93 (0.46)	4.28	**0.01**[&]	0.00	0.98	2.55	0.11	0.42	0.66	4.55	0.01
Recognition list A	13.05 (0.18)	13.05 (0.18)	11.01 (0.46)	0.13	0.88	3.31	0.07	5.63	0.02	0.08	0.92	0.17	0.85
Recognition list B	7.00 (0.58)	6.75 (0.23)	4.01 (0.58)	11.08	0.00	1.08	0.30	0.81	0.37	0.61	0.55	0.01	0.99
Visual Reprod. 1 Immediate recall	37.36 (36.06, 38.55)	35.97 (35.44, 36.48)	35.26 (33.79, 36.56)	1.38	0.25	1.39	0.24	19.46	0.000	0.49	0.62	1.08	0.34
Visual Reprod. 2 Delayed recall	35.18 (33.50, 36.65)	34.12 (33.46, 34.75)	32.67 (30.66, 34.36)	0.40	0.67	2.17	0.14	23.82	0.001	1.38	0.25	0.24	0.79
Visual Reprod. Immed-delayed	0.03 (0.81)	2.57 (0.31)	3.27 (0.76)	0.18	0.83	0.42	0.52	4.48	0.04	0.27	0.76	0.18	0.38
RBMT story Immediate recall	9.51 (0.66)	9.08 (0.25)	7.65 (0.79)	1.01	0.37	3.69	0.06	21.22	0.000	0.11	0.89	1.20	0.30
RBMT story Delayed recall	8.93 (0.63)	7.92 (0.24)	6.9 (0.76)	0.34	0.71	2.07	0.15	20.41	0.000	0.14	0.87	0.43	0.65
STORY IMM-DEL	0.58 (0.34)	1.14 (0.13)	0.75 (0.41)	1.13	0.32	1.08	0.30	0.27	0.61	0.00	0.99	1.06	0.35
RBMT standardised score	131.98 (11.91)	104.17 (4.56)	88.69 (14.28)	2.99	**0.05**[§]	0.18	0.67	3.59	0.06	1.34	0.26	1.71	0.18
General Mental ability													
Block Design	12.84 (0.55)	11.08 (0.21)	11.34 (0.56)	4.12	**0.02**[¤]	4.96	0.03	29.14	0.00	1.78	0.17	3.73	0.03

Post hoc evaluation of main effects by the method of Least Squares Difference

^Unadjusted median (25^{th}, 75^{th} percentile)

[*]= HR≠C, HR=P, P=C

[#]=There were no individual group differences on univariate analysis

[&]= HR=C, HR≠P, P≠C

[§]= HR≠C, HR=P, P≠C

[¤]= HR≠C, HR=P, P≠C

5.5.7. CPT-IP analyses controlling for NART

An identical analysis was conducted for the CPT-IP as outlined Tables 5.2 and 5.3 but with NART as a covariate. The analysis controlling for NART for the distraction conditions is presented in Table 5.5, and in Table 5.6 the analysis of the effect of speed controlling for NART is presented.

5.5.7.1. Distraction conditions

Log Randoms

Controlling for NART in the distraction condition removed all significant main effects for group and the interaction effects. There was a significant a main effect for NART.

D prime

Controlling for NART the main effect for group remained for the patient group to have significantly lower d'prime scores than either the high-risk or control group. No significant interactions were noted. There was a significant effect of NART.

Log Beta

No significant main effects or interactions were found for log beta in the distraction conditions.

5.5.7.2. Speed conditions

Log Randoms

An analysis was conducted involving the ranked co-variate (NART) and the ranked dependent variable (Conover and Inman, 1982). Controlling for NART only a trend remained for the patients to make more random errors than the other groups. There was a significant effect of NART on log randoms. There was no main effect of either stimulus or speed. A group by speed interaction was observed and this interaction is displayed in Figures 5.2a and 5.2b.

D Prime

Controlling for NART the same group difference emerged as in the analysis without the co-variate. The patient group had significantly lower d prime scores than either the high-risk group or the controls on this measure. There was a significant main effect for NART. No significant interactions were noted.

Log Beta

No significant main effects or interactions were found for log beta in the distraction conditions.

Fig. 5.2a. Speed by group interaction

for CPT-IP numbers log random

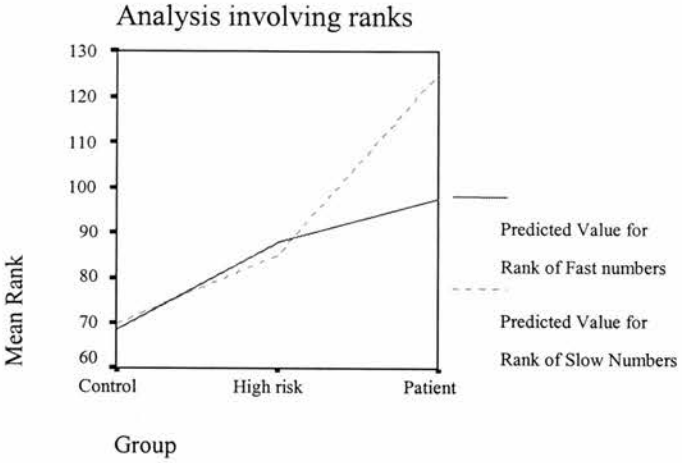
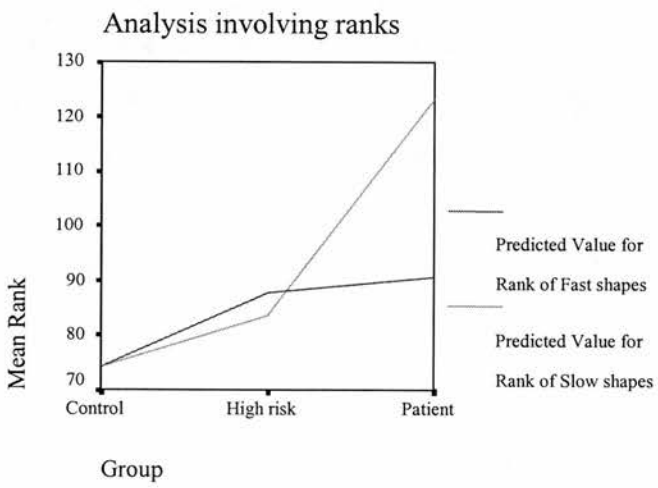


Fig. 5.2b Speed by group interaction

for CPT-IP shapes, log random



Figures 5.2a and 5.2b CPT-IP group by speed interactions for log randoms (numbers and shapes) adjusted for NART

Table 5.5. CPT-IP distraction and stimulus conditions; marginal unadjusted means presented.

		High Risk N=124	Control N=29	Patient N=15	Group F	Group P	Stimulus F	Stimulus P	NART F	NART P	Distraction F	Distraction P
Log Randoms	No distraction											
Fast Numbers	Distraction	0.46 (0.62)	0.25 (0.52)	0.56 (0.61)								
	No distraction	0.64 (0.62)	0.46 (0.63)	1.03 (0.89)	1.43[&]	0.24	0.62	0.43	13.69	0.00	0.01	0.92
Fast Shapes	Distraction	0.56 (0.66)	0.40 (0.55)	0.66 90.84)								
		0.60 (0.73)	0.39 (0.56)	0.94 (0.74)								
D Prime	No distraction											
Fast Numbers	Distraction	1.76 (0.83)	1.93 (0.89)	1.22 (0.58)								
	No distraction	1.64 (0.86)	1.67 (0.85)	0.99 (0.68)	5.21	0.01[a]	0.006	0.94	38.58	0.00	0.17	0.68
Fast Shapes	Distraction	1.69 (0.71)	1.95 (0.62)	1.15 (0.30)								
		1.90 (0.89)	2.28 (0.86)	1.22 (0.56)								
Log Beta	No distraction											
Fast Numbers	Distraction	-0.12 (0.74)	-0.06 (0.53)	0.04 (0.39)								
	No distraction	-0.32 (0.68)	-0.37 (0.75)	-0.27 (0.82)	0.53	0.59	0.03	0.87	0.38	0.54	2.64	0.11
Fast Shapes	Distraction	-0.19 (0.82)	-0.18 (0.96)	-0.06 (0.45)								
		-0.24 (0.79)	-0.13 (0.62)	0.02 (0.46)								

None of the following interactions were significant, stimulus*NART, stimulus * group; distraction* group; distraction*NART, stimulus*distraction*NART, stimulus*distraction* group, and were not presented in the Table for ease of reading.

[&]Conover and Inman Analysis of covariance using ranks.

[a]C=HR, HR≠P, C≠P

Table 5.6 CPT-IP speed and stimulus conditions; marginal unadjusted means presented

		High Risk N=124	Control N=29	Patient N=15	Group F	Group P	Stimulus F	Stimulus P	NART F	NART P	Speed F	Speed P
Log Randoms	Fast	0.46 (0.62)	0.25 (0.52)	0.56 (0.61)								
Numbers	Slow	0.35 (0.55)	0.22 (0.50)	0.98 (0.96)								
	Fast	0.56 (0.66)	0.40 (0.55)	0.66 (0.84)	2.86	0.06[&]	0.01	0.95	18.20	0.00	2.0	0.16
Shapes	Slow	0.48 (0.72)	0.34 (0.55)	1.06 (0.88)								
D Prime	Fast	1.76 (0.83)	1.93 (0.89)	1.22 (0.58)								
Numbers	Slow	2.24 (0.96)	2.33 (1.10)	1.36 (0.86)								
	Fast	1.69 (0.71)	1.95 (0.62)	1.15 (0.30)	5.68	0.01[£]	0.03	0.87	40.13	0.00	0.05	0.82
Shapes	Slow	2.28 (0.94)	2.59 (0.80)	1.61 (0.80)								
Log Beta	Fast	-0.32 (0.68)	-0.37 (0.75)	-0.27 (0.82)								
Numbers	Slow	-0.26 (0.87)	-0.24 (0.76)	0.10 (0.71)								
	Fast	-0.25 (0.79)	-0.13 (0.62)	0.02 (0.46)	0.58	0.56	0.93	0.33	0.30	0.58	2.48	0.12
Shapes	Slow	-0.24 (0.94)	-0.27 (0.97)	-0.23 (0.82)								

None of the following interactions were significant, stimulus*NART, stimulus * group; speed* group; speed*NART, stimulus*speed*NART, stimulus*speed* group, and were not presented in the Table for ease of reading. Post Hoc Scheffe test: [a] C≠P, HR ≠P, HR=C.

[&]Trend for C≠P, HR≠P, Conover and Inman Analysis of covariance using ranks, patient group significantly different from controls (p=0.02), and high-risk subjects (p=0.03).

There was a speed by group interaction (Hotellings T, F=7.95; p=0.001).

[£]C≠P, HR≠P, HR=C

5.5.8. Summary of univariate analyses controlling for NART

In the executive function domain, the HR group made significantly more type B errors than the Patients of Controls. In the domain of learning and memory, a group effect was observed for the RAVLT trial one, but was accompanied by a NART by group interaction and on investigation the NART was less associated with this measure in the HR group compared to the other two groups. The patients had poorer recall scores for list B of the RAVLT and gained fewer words across sucessive trials than the other groups. For the total RBMT standardised score, the HR and Patient groups had significantly lower scores than the Controls, with the Patients having the lowest scores. On the block design subtest, the HR and Patient groups had significantly lower adjusted scores than the Controls. A NART by group interaction indicated that the HR and Patients showed greater variability on this test than the controls.

In terms of the CPT-IP adjusted scores, the patients had significantly lower d' scores than either the HR or Controls in the distraction condition. No group effects were noted for log randoms or log beta. In the speed condition, the Patients had significantly lower d' values than the other groups and there was a trend for Patients to make more random errors than the other groups.

5.6. MULTIVARIATE ANALYSIS

We were interested in investigating the possible presence of neuropsychological deficits among the high-risk group, compared to the controls and patients. Deficits in any area of function would be important as they could be related to a number of different factors about which we already have some information including genetic liability, clinical state, and structural brain scan measurements. Such deficits may be especially marked in some subgroups (the high-risk group was recognised to be a likely heterogeneous group). Neuropsychological deficits in this young well population were expected to be subtle, otherwise such individuals would likely be presenting for treatment of clinically relevant impairments that could be disruptive to vocational and social functioning. It was for these reasons that it was considered necessary to evaluate the data using a univariate approach to search for subtle differences between the groups, especially when dealing with such a valuable and rare group as the high-risk sample. The univariate analysis was not corrected for multiple comparisons. Many areas of

functioning were examined but each was decided on apriori, and differences predicted apriori. The interest was in assessing all variables singularly and not just a general overall null hypothesis (Perneger, 1998). Indeed if any one test was found to discriminate between the groups in a consistent manner it would be considered a very useful screening tool indeed. However, the issue of multiple testing remains a sufficiently thorny one and the need for multivariate techniques was apparent.

Two such techniques were employed to help deal with the large volume of data generated in the study. The first multivariate technique used was the technique of factor analysis, the second approach to data reduction involved computing standardised z-scores using the control mean and standard deviation and averaging the z-scores for the individual tests in each domain, to create a single standardised averaged z-score per domain of function. The CPT was not included in the factor analysis, as it was analysed using a multivariate technique according to the method outlined by Cornblatt et al., (1988), and was analysed as a stand alone test. However, standardised z-scores were computed for D'prime, log beta, and log random measures.

5.6.1. FACTOR ANALYSIS

The steps taken to prepare the data for factor analysis are outlined in detailed in Chapter 4, the exploratory data analysis section.

The following variables were entered into the factor analysis:

WAIS-R FSIQ

WAIS-R VIQ

WAIS-R PIQ

WAIS-R Vocabulary test

WAIS-R Arithmetic

WAIS-R Block Design

WAIS-R Digits forwards

WAIS-R Digits backwards

WAIS-R Digit symbol substitution test

NART

Spot the Word

Speed of Comprehension

RAVLT (total of trials 1 to 5)

RAVLT recall of trial 1

RAVLT delayed recall

RBMT story immediate

RBMT story delayed

WMS-R Visual Reproductions immediate recall

WMS-R Visual Reproductions delayed recall

Verbal Fluency FAS

Verbal Fluency Animals

Stroop; incongruous condition

RBMT standardised score

Token test, total score

Hayling Sentence Completion test, total errors

Hayling Sentence Completion Test, errors A

Hayling Sentence Completion Test, errors B

Time taken to complete section A, on the Hayling

Time taken to complete section B, on the Hayling

The method of principal components analysis (PCA) was used to extract the factors. The component matrix from the PCA was subjected to a varimax rotation. This was to allow for the identification of orthogonal factors. It was decided that this would be the best method for this data to allow uncorrelated factors to emerge. The factor analysis produced a six factor solution, with eigenvalues greater than 1 explaining a cumulative total of 67.71% of the variance in the data.

5.6.1.1. Interpretation of the factor analysis

The rotated factor solutions along with the variable loadings are presented in Table 5.7a and the Eigenvalues for each factor and the amount of variation explained by each is outlined in Table 5.7b. Variables appear once only, and variables with loadings greater than 0.3 were considered significant. The factors were interpreted in keeping with the guidelines for simple structure factor solutions, where only one loading on any factor

for each variable is considered (Hair et al., 1992). Factor scores were retained for further analysis. A high factor score shows that an individual possesses a characteristic represented by the factor to a high degree. Factor scores are based on the correlations with all the variables in the factor and these correlations are likely to be less than 1.0 the scores are only approximations of the factors and as such are error prone indicators of the underlying factors. Also a degree of subjectivity is demanded in the interpretation of the factors. Hair et al., (1992) caution that reliability is a real problem in that factor analysis starts with a set of imperfect data, like any other statistical technique. When the data change because of changes in the sample, the data gathering process, or the numerous kinds of measurement errors, the result of the analysis also change. While the results of a single factor analysis look plausible, it is important to emphasise that plausibility is no guarantee of validity or stability (Hair et al., 1992, pg 256).

Factor one

The variables loading on factor one were Digits Forwards, Digits Backwards, VIQ, NART, Arithmetic, Vocabulary, Spot the Word, and FSIQ. These are mainly tests of verbal intelligence/ ability. Digits and arithmetic sub-tests are known to load highly on attention and concentration abilities. Also education appears to have a strong effect on this factor. This factor was interpreted as reflecting verbal ability.

Factor two

The tests comprising factor two were the immediate, and delayed recall Visual Reproduction trials of the WMS-R, Block Design, and PIQ. This factor was interpreted as representing visuo-spatial/performance ability and visual memory.

Factor three

Factor three loaded on the immediate and delayed recall sections of the RBMT story, and negatively on time to complete section A of the Hayling Sentence Completion test suggesting that higher scores on the factor are related to faster times. Time to sentence completion on section A of the Hayling test could have a memory component, memory for logical material/ semantic memory. The speed with which a sentence is completed would be related to how easy the information was to access. So this factor may be related to memory for meaningful information.

Factor four

This factor is exclusively comprised of measures from the Hayling Sentence Completion test, total errors, a composite of errors A and errors B and also included time B. This factor is related to response suppression. Time to complete section B is related to the accuracy of response suppression.

Factor five

Factor five loads highly on the Stroop, incongruous condition, the Speed of Comprehension, Digit Symbol, FAS, Animals, and the Token Test. Factor 5 appears to represent executive function, those requiring effective concentration and attention for successful completion. While many of these tests are related to language ability, the fact they appear together seems to suggest that it is the attention/distractibility aspect of these tests that this factor taps into. Stroop involves response conflict and is affected greatly by failures of attention. Verbal fluency also has a distractibility component. The Token Test, while being a test of aphasia, depends on the subjects' ability to concentrate and remember the commands given to them, as failure to concentrate and remember the required moves will result in failure. Digit symbol test and the speed of comprehension require attention and concentration and an element of effective motor speed for successful completion. It could be related to working memory.

Factor six

The final factor was interpreted as a learning/memory factor comprising mostly the Rey Auditory Verbal Learning Test measures including the RAVLT total recall (sum of trials I to V), RAVLT I, RAVLT delayed recall condition. This factor included the Rivermead Behavioural Memory test also.

Table 5.7a. Rotated factors: variables with loadings greater than 3, variables appear once (in factor with highest loading).

FACTOR 1		FACTOR 2		FACTOR 3		FACTOR 4		FACTOR 5		FACTOR 6	
Digits forwards	0.793	Delayed Visual Reproductions	0.797	Story immediate	0.759	Total Hayling errors	0.97	Stroop3	-0.72	RAVLT I-V	0.834
Digits back	0.729	Blocks	0.794	Story delayed	0.750	Errors A	0.853	Speed of comprehension	0.67	RAVLT I	0.732
Verbal IQ	0.685	Immediate Visual Reproductions	0.784	Lnhtime A	-0.539	Errors B	0.797	Digit symbol	0.62	RAVLT delayed	0.721
Nart	0.615	Performance I .Q.	0.609			Lnhtimeb	0.634	FAS	0.56	RBMT	0.482
Arithmetic	0.600							Animals	0.43		
Vocabulary	0.590							Token test	0.38		
Spot the word	0.560										
FSIQ	0.550										

Table 5.7b. Total variance explained by each factor.

Factor	Eigenvalues	Percentage of variance explained	Cumulative %	Percentage of variance explained after rotation	Rotated sums of squares
1	11.23	38.71	37.71	14.13	4.10
2	2.67	9.20	47.92	13.49	3.91
3	1.90	6.56	54.48	10.15	2.94
4	1.52	5.24	59.72	10.07	2.92
5	1.28	4.43	64.15	10.02	2.90
6	1.03	3.56	67.71	9.85	2.86

5.6.1.2. Analysis of the factor scores

All factor scores were subject to normality checks and were found to be acceptably normally distributed according to the criteria outlined in chapter 4. A full factorial multivariate analysis of variance was conducted with group and gender as factors in the model. The initial group comparisons for each of the six factors are presented in 5.8. There were no significant differences found between the groups in terms of factor one. Significant group differences were found on factor 2 (spatial ability memory/PIQ), with the controls achieving significantly higher scores on this measure than either the high-risk group of the patients. The patients and the high-risk subjects did not significantly differ. The same pattern emerged for factor three, with controls having significantly higher factor scores than either the high-risk group or the patients. No significant group differences were observed for factor 4. On factor 5 the control group and the high-risk group had significantly higher factor scores than the patients. The same was true for factor six again with controls and the high-risk group scoring significantly better than the patients.

The factor scores were re-analysed by means of a full factorial model, multivariate analysis of co-variance with group and gender as factors in the model and NART as the co-variate (the analysis of co-variance was not conducted for factor one as it included NART). The results are shown in Table 5.9. There was a main effect for NART for factors 2, 3, and 5. For factor 2 controls the controls had significantly higher factor scores than the high-risk group. There were no observed significant group differences for factors 3 or 4. On factor 5 the patient group had significantly lower factor scores than the high-risk group or the controls. On factor 6 again the patients had significantly lower factor scores than the controls or the high-risk group. There was a trend for the high-risk group and the controls to differ on this factor.

Table 5. 8. Overall differences across the groups in terms of each factor

	High Risk Mean (sd)	Control Mean (sd)	Patients Mean (sd)	Sex F	P	Group F	P	Group * Sex F	P	Post Hoc Tests Group differences
FACTOR 1	0.02 (0.98)	0.06 (1.04)	-0.20 (1.05)	2.19	0.14	0.85	0.43	0.34	0.71	ND
FACTOR 2	-0.09 (0.94)	0.52 (1.14)	-0.16 (0.97)	4.93	0.03	5.77	0.004	1.58	0.21	HR=P, C≠P, HR≠C
FACTOR 3	-0.06 (1.02)	0.43 (0.94)	-0.20 (0.82)	3.22	0.07	4.37	0.01	0.39	0.67	HR=P, C≠P, HR≠C
FACTOR 4	0.02 (1.03)	-0.12 (1.01)	0.03 (0.83)	2.64	0.11	0.27	0.76	2.69	0.07	ND
FACTOR 5	0.08 (0.93)	0.22 (0.99)	-0.73 (1.10)	0.81	0.67	8.59	0.00	0.06	0.94	HR≠P, C≠P, HR=C
FACTOR 6	0.04 (0.93)	0.36 (0.91)	-0.66 (1.20)	8.79	0.003	7.91	0.00	0.21	0.81	HR≠P, C≠P, HR=C(P=0.07)

Table 5. 9. Overall differences across the groups for factors 2 to 6 with NART as a co-variate

	High Risk Mean (sd)	Control Mean (sd)	Patients Mean (sd)	Sex F	P	Group F	P	Group * Sex F	P	NART		Post hoc tests
FACTOR 1	0.02 (0.98)	0.06 (1.04)	-0.20 (1.05)	2.19	0.14	0.85	0.43	0.34	0.71			
FACTOR 2	-0.06 (0.08)	0.34 (0.16)	-0.09 (0.19)	6.29	0.01	2.58	0.08	1.20	0.30	15.75	0.00	HR=P, C=P, HR≠C
FACTOR 3	-0.01 (0.08)	0.27 (0.17)	-0.12 (0.20)	3.50	0.06	1.39	0.25	0.54	0.58	14.38	0.00	ND
FACTOR 4	0.01 (0.08)	-0.14 (0.18)	-0.05 (0.21)	3.22	0.07	0.33	0.72	2.85	0.06	0.33	0.57	ND
FACTOR 5	0.10 (0.08)	0.06 (0.17)	-0.56 (0.20)	0.66	0.42	5.10	0.01	0.01	0.99	12.96	0.00	HR≠P, C≠P, HR=C
FACTOR 6	0.01 (0.08)	0.35 (0.17)	-0.51 (0.20)	7.73	0.01	5.36	0.01	0.17	0.85	0.08	0.76	HR≠P, C≠P, HR=C (0.07)

5.6.1.3.Summary of unadjusted analyses of factor scores

Controls had significantly greater factor scores than the HR and Patient groups on factor 2 (visuo-spatial/performance ability and visual memory) and factor 3 (memory for meaningful information/semantic memory). Control and HR groups had significantly higher factor scores than Patients on factor 5 (attention/distractability) and factor 6 (learning/memory) with a trend for the controls to have higher factors than the HR group on this factor.

5.6.1.4. Summary of analyses of factor scores adjusting for the NART

With NART as a co-variate for factors 2 to 6 the Controls had higher scores then the HR, but not the Patients, on factor 2 (visuo-spatial/performance ability and visual memory). Both controls and HR were significantly better than the Patients on factors 5 and 6 and again there was a trend for Controls to have higher factor scores than the HR group on this factor.

5.6.2. Composite standardised Z scores

According to the methods outlined in chapter 4 (section 4.5) standardised z scores were produced for each variable using the control group mean and standard deviation. The standardised z scores were then averaged for each domain of function to compute a single composite score for that area. Composite scores for executive function (COMP1EX) included the Hayling total errors, time A, time B, Stroop incongruous condition, FAS, and animals. The composite for mental control/encoding (COMP2MC) included digits forward, digits backward, and arithmetic. Perceptual motor speed was comprised solely of the digit symbol subtest and so is technically not a composite score but for continuity it is presented with the other composites (COMP3PMS). Verbal ability and language composite comprised the token test, speed of comprehension, and vocabulary (COMP4LAN). The final composite of learning and memory variables was made up of the RBMT standardised scores, the RAVLT total of trial I to V, RAVLT delayed recall, visual reproductions immediate and delayed, and RBMT story immediate and story delayed. The results of the analysis using the composite scores are presented in Table 5.10 and 5.11. Multivariate analyses of variance were conducted both with and without NART as the co-variate. Given the

known effect of IQ on the tests, it was decided that the NART should be controlled in the analysis and the results are presented in 5.11.

5.6.2.1. Composite scores analysed without NART as a covariate

The results are presented in graph form in Figure 5.3 and in Table 5.10. All groups differently significantly form each other on all of the 5 composite scores with one exception; on the mental control/encoding composite the HR and control groups did not significantly differ. In all cases the results were in the hypothesised direction. The HR groups mean standardised scores were below that of the control group and in turn the patient group had lower mean standardised scores than the high-risk group.

Figure 5.3. Plot of mean z-scores for each composite across the groups

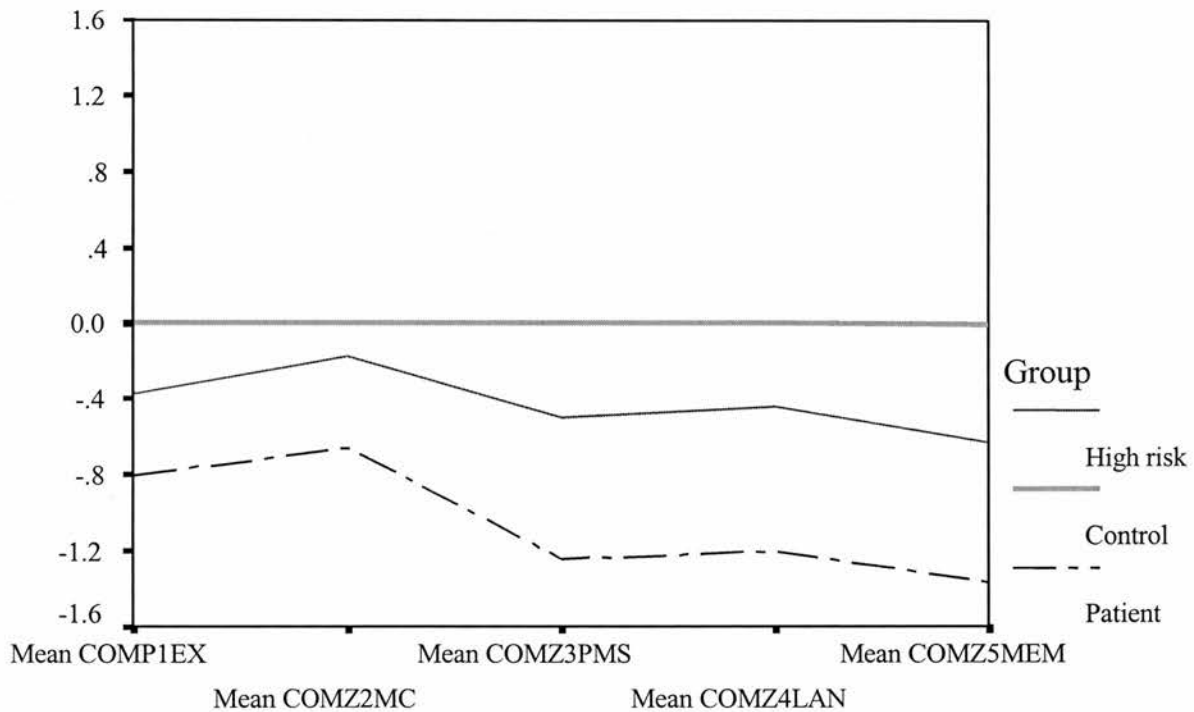


Figure 5.3 Plot of unadjusted composite Z scores

In Figure 5.3 the means of the composite scores are presented without adjustment for NART. COMPEX=the composite of executive functions, COMZ2MC=the composite score for mental control/encoding, COMZ3PMS=the composite score for perceptual motor speed, COMZ4LAN= composite score for language tests, COMZ5MEM= the composite scores for learning and memory tests.

5.6.2.2. Composite scores analysed with NART as a covariate

The composite scores adjusted for NART were computed as outlined in chapter 4, according to the method suggested by Chapman and Chapman (1989).

The patients performed significantly more poorly than both the controls and the high-risk group in terms of the executive function composite. The high-risk group and the patients differed significantly on composite 2, mental control/encoding measure. In terms of perceptual motor speed, the high-risk group and the patient group had significantly lower Z scores than the controls. For the language composite the patients had significantly lower scores than the other groups. All groups differed significantly from each other on the memory composite.

Figure 5.4. Plot of adjusted mean z-scores for each composite across the groups

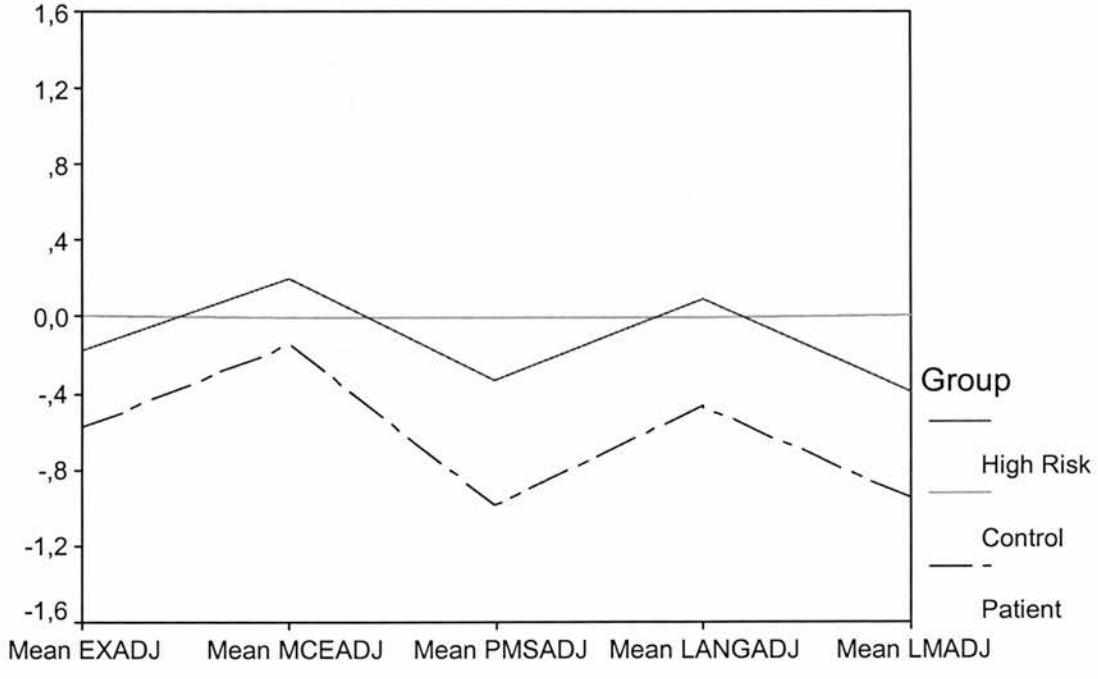


Figure 5.4. plot of adjusted composite Z scores

In Figure 5.4 the means of the composite scores are presented with adjustment for NART. EXADJ=the composite of executive functions, MCEADJ=the composite of adjusted scores for mental control/encoding, PMSADJ=the composite of adjusted scores for perceptual motor speed, LANGADJ= the composite of adjusted scores for language tests, LMADJ= the composite of adjusted scores for learning and memory tests.

Table 5.10. Means and standard errors from the comparison across groups of each of the composite scores, without controlling for NART

Functions	High Risk N=150 Mean (se)	Control N=34 Mean (se)	Patient N=24 Mean (se)	Group F	P	Sex F	P	Post Hoc Tests
Executive	-0.35 (0.05)	0 (0.11)	-0.81 (0.12)	13.66	0.00	0.001	0.99	HR≠P, C≠P, HR≠C
Mental control/ encoding	-0.16 (0.06)	0 (0.14)	-0.70 (0.15)	6.93	0.001	5.86	0.02	HR≠P, C≠P, HR=C
Perceptual motor speed	-0.50 (0.08)	0 (0.17)	-1.18 (0.19)	10.88	0.00	2.59	0.11	HR≠P, C≠P, HR≠C
Language	-0.41 (0.07)	0 (0.13)	-1.22 (0.17)	15.45	0.00	0.47	0.49	HR≠P, C≠P, HR≠C
Learning and Memory	-0.63 (0.06)	0 (0.10)	-1.36 (0.15)	22.33	0.00	0.01	0.90	HR≠P, C≠P, HR≠C

All models were significant.
Hotellings T, group effect F=5.43, df 10, p=0.00 sex F=3.58, df 5, p=0.004, group by sex F=0.87, df 10, p=0.57
There were no significant group by gender interactions.

Table 5.11. Adjusted means and standard errors from the comparison across groups of each of the composite scores adjusted for NART

Functions	High Risk N=150 Mean (se)	Control N=34 Mean (se)	Patient N=24 Mean (se)	Group F	P	Sex F	P	Post Hoc Tests
Executive	-0.18 (0.57)	0 (0.61)	-0.58 (0.37)	7.37	0.001	0.02	0.89	HR≠P, C≠P, HR=C
Mental control/ encoding	0.21 (0.68)	0 (0.80)	-0.15 (0.67)	4.39	0.01	12.02	0.001	HR=P, C=P, HR=C
Perceptual motor speed	-0.33 (0.94)	0 (0.96)	-0.99 (0.98)	6.75	0.001	2.15	0.14	HR≠P, C≠P, HR=C
Language	0.09 (0.82)	0 (0.81)	-0.47 (1.02)	3.95	0.02	0.00	1.00	HR≠P, C≠P, HR=C
Learning and Memory	-0.39 (0.72)	0 (0.64)	-0.95 (0.79)	12.56	0.000	0.30	0.58	HR≠P, C≠P, HR≠C

All models were significant.
Hotellings T, group effect F=4.22, df=10, p=0.00, sex F=4.18, df=5, p=0.001, group by sex F=1.27, df=10, p=0.57
There were no significant group by gender interactions.

5.6.2.3.Summary of the analyses of unadjusted composite scores

There were significant differences between all groups in the expected direction (Controls >HR>Patients) on all composites except on mental control/encoding, where there was no difference between the HR and control group but both had higher scores than the patients.

5.6.2.4. Summary of the analyses of composite scores controlling for NART

Controlling for NART no group differences were observed on mental control/encoding. The Controls and the HR groups were significantly better than the Patients on the composite of executive function, perceptual motor speed, and language. All groups differed significantly from each other in the predicted direction on the learning and memory composite.

5.6.2.5. CPT-IP Standardised Z-scores

Standardised Z scores was produced for the 3 CPT-IP measures overall, log randoms, D'prime, and log beta and for each measure individually for numbers and shapes. For the CPT, the z scores were not controlled for NART in the way described above, after the method of Chapman and Chapman (1978), instead NART was adjusted in the analysis by its addition into the model as a covariate. The overall composite scores for each measure unadjusted for NART are presented in Table 5.12. Analysis controlling for NART are presented in Table 5.13. A multivariate analysis of variance, full factorial model was conducted. The results from the two analyses are very similar. There was no group or NART effect for the log beta composite z scores. There was a significant co-variate effect for NART on both the log random, and D'prime composites. There was no gender by group interaction. Both with and without controlling for NART, the patient group had significantly lower z scores than the high-risk and control groups for D' prime and had significantly higher scores for log random, indicating that they make more random errors than the other groups.

The results of the analysis of the composite scores separated out into numbers and shapes and unadjusted for NART are presented in Table 5.14. A multivariate ANOVA

was conducted. Significant group effects were noted for log random, and D'prime composites for both numbers and shapes but not for log beta. No group by gender interactions were observed. For the log-randoms, shapes composite, the patients were significantly poorer than the controls. For log random numbers both the patients and the high-risk group had significantly lower z scores than the controls. For D'prime, shapes and numbers, patients had significantly lower scores than both of the other groups. On all measures, the controls had higher z scores, followed by the high-risk group, with patients consistently having the lowest scores.

The results of the analysis adjusting for NART are given in Table 5.15. Adjusting for NART all significant group differences disappeared. Again NART had no effect on log Beta measures but had a significant effect on both log randoms and D prime measures. No significant interactions were observed.

5.6.2.6.Summary of unadjusted CPT-IP composite score analysis

For the combined numbers and shapes composites, the controls and the HR groups made significantly fewer random errors and had significantly higher d' scores than the patients. In the analyses of the separate numbers and shapes composites, the Controls made significantly less random and had significantly higher d' values compared to Patients for numbers and shapes. The HR group made significantly more random errors than the Controls on the numbers composite only.

5.6.2.7. Summary of CPT-IP composite score analysis adjusting for NART

For the combined numbers and shapes composites, the only significant group effect was noted for the composite of d' values. The Patients had significantly lower d' composite values than the other groups. In the analyses of the separate numbers and shapes composites with NART as a covariate, no significant group effects were observed.

Table 5.12. Composite CPT z scores for d'prime, z ln randoms, and z log beta, for shapes, numbers, slow/fast, and distraction/non distraction conditions.

	High Risk N=126 Mean (sd)	Control N=30 Mean (sd)	Patients N=15 Mean (sd)	SEX		GROUP		GROUP*GENDER		POST HOC TESTS
				F	P	F	P	F	P	
Z-Random	0.31 (0.95)	0.00 (0.78)	0.96 (1.32)	0.21	0.64	4.21	0.02	0.88	0.42	HR≠P, C≠P, HR=C
Z-d'prime	-0.26 (0.83)	0.00 (0.75)	-1.04 (0.53)	1.43	0.23	8.21	0.00	0.11	0.90	HR≠P, C≠P, HR=C
Z-Log Beta	-0.04 (0.79)	-0.00 (0.67)	0.19 (0.61)	2.11	0.15	0.27	0.77	0.30	0.74	ND

Table 5.13. Composite CPT z scores for z d 'prime, z random, z log beta, for shapes, numbers, slow/fast, distraction/non distraction conditions; adjusted for NART.

	High Risk N=124 Mean (se)	Control N=29 Mean (se)	Patients N=15 Mean (se)	SEX		GROUP		GROUP*GENDER		NART	
				F	P	F	P	F	P	F	P
Z-Random	0.27 (0.08)	0.12 (0.17)	0.78 (0.24)	0.03	0.86	2.45	0.09	0.39	0.68	21.60	0.00
Z-d'prime	-0.21 (0.06)	-0.20 (0.14)	-0.90 (0.20)	1.32	0.25	5.65	0.01*	0.11	0.90	41.61	0.00
Z-Log Beta	-0.02 (0.07)	-0.03 (0.150	0.14 (0.21)	2.15	0.14	0.29	0.75	0.27	0.76	0.74	0.39

* P≠C, P≠HR, HR=C

Table 5.14. CPT-IP composite scores; numbers and shapes, not adjusted for IQ

	High Risk N=126 Mean (sd)	Control N=30 Mean (sd)	Patients N=15 Mean (sd)	SEX F	SEX P	GROUP F	GROUP P	GROUP*GENDER F	GROUP*GENDER P	POST HOC TESTS
Z-Random shapes	0.30 (1.10)	0.00 (0.83)	0.92 (1.10)	0.49	0.48	3.10	0.05	0.86	0.42	HR=P, C≠P, HR=C
Z-Random numbers	0.32 (0.92)	-0.00 (0.84)	1.00 (1.36)	0.19	0.89	4.58	0.01	0.72	0.49	HR=P, C≠P, HR≠C
Z d'prime shapes	-0.42 (1.02)	0.00 (0.94)	-1.25 (0.55)	2.87	0.09	8.06	0.00	0.68	0.51	HR≠P, C≠P, HR=C
Z d'prime numbers	-0.11 (0.85)	-0.00 (0.89)	-0.83 (0.66)	0.11	0.74	5.06	0.01	0.36	0.70	HR≠P, C≠P, HR=C
Z Log beta shapes	-0.05 (0.87)	-0.00 (0.79)	0.13 (0.59)	0.42	0.52	0.21	0.81	0.29	0.75	ND
Z log beta numbers	-0.02 (0.92)	0.00 (0.73)	0.25 (0.81)	3.54	0.06	0.22	0.81	1.20	0.30	ND

Table 5.15. CPT-IP composite scores; numbers and shapes, adjusted for IQ

	High Risk N=124 Mean (se)	Control N=29 Mean (se)	Patients N=15 Mean (se)	SEX F	SEX P	GROUP F	GROUP P	GROUP*NART F	GROUP*NART P	NART F	NART P
Z-Random shapes	0.25 (0.09)	0.00 (0.24)	0.70 (0.30)	0.31	0.58	0.78	0.46	0.69	0.50	6.96	0.01
Z-Random numbers	0.28 (0.08)	-0.05 (0.21)	0.79 (0.26)	0.04	0.84	0.81	0.45	0.60	0.55	6.39	0.01
Z D'prime shapes	-0.37 (0.08)	-0.20 (0.21)	-1.11 (0.26)	2.92	0.09	0.14	0.87	0.13	0.87	13.33	0.00
Z D'prime numbers	-0.05 (0.07)	-0.15 (0.19)	-0.79 (0.23)	0.02	0.88	0.23	0.80	0.47	0.62	6.89	0.01
Z Log beta shapes	-0.05 (0.08)	-0.02 (0.20)	0.03 (0.25)	0.33	0.57	0.40	0.67	0.35	0.70	0.04	0.85
Z log beta numbers	-0.00 (0.08)	-0.02 (0.21)	0.07 (0.26)	3.74	0.05	0.79	0.45	0.72	0.49	0.03	0.87

5.7. General summary of Chapter Five

Compared to controls broadly based intellectual deficits were observed in measures of current and pre-morbid intellectual functioning in the HR and Patient groups. Patients showed a significant decline in intellectual performance from pre-morbid levels compared to the other groups. In the unadjusted analyses deficits were observed in all domains of functioning in the Patient group compared to Controls, and in all but the mental control /encoding domain for the HR group compared to Controls. Controlling for NART deficits in ***executive function, learning and memory***, and ***block design (visuo-spatial task)*** were evident in the HR and Patient groups compared to controls.

Patients had lower CPT-IP ***d'*** values and made more ***random errors*** compared to the other groups in the unadjusted analyses. Patients had lower ***d'*** values on the CPT-IP than the other groups in conditions involving distraction, and different speeds of presentation, for shapes and numbers conditions when NART was controlled in the analyses.

Multivariate analyses controlling for NART

In the multivariate factor analysis, controlling for IQ, group deficits were noted in ***learning and memory*** (C>P; C trend for>HR), ***visuo-spatial/performance ability*** (C>HR), and ***attention/ distractability*** (C & HR>P).

In terms of the composite scores controlling for NART, Patients showed deficits in all domains except mental/control encoding, compared to HR and Controls. All groups differed in the predicted direction on the ***learning and memory composite*** (C>HR>P).

In the analyses involving the CPT-IP composites controlling for NART, the Patients had significantly lower ***d'*** scores than the other two groups.

5.8. DISCUSSION

The analyses of the baseline assessment showed that in terms of both current and pre-morbid IQ, the control group performed significantly better than the HR group who in turn performed significantly better than the patients group. The difference between the Patients and the controls (>15 points) would be considered clinically relevant (Lezak, 1995), this was not the case for the HR group / control group comparison but there was an obvious decrement in all aspects of HR IQ compared to controls and this supports the findings of other studies. Sex differences were found for FSIQ but in the absence of a gender by group interaction it was felt that there was no reason to analyse the data separately for males and females.

The IQ differences are not due to an unrepresentative elevation of IQ in the controls as the IQ estimates for this group were similar to those quoted for a normal sample of British persons (Crawford et al., 1995). This difference in FSIQ of 7/8 points is a similar figure to that reported by Done et al. (1994) in the British Cohort study of 8/9 points to characterise the average difference in performance of a pre-schizophrenic population compared to controls on a range of neuropsychological tests.

It has been remarked that IQ and social class 'have proven to be a pervasive and troublesome sources of confusion in interpreting research results, whether they should be controlled as sources of contamination in analysing statistical results, or should be considered as important precursors of schizophrenic disorders worthy of study in their own right'(Watt, 1984, page, 577). In the samples reported here, there was no difference between the groups in terms of social class at birth and so this would not appear to be a mediating factor between IQ and group. IQ is known to be affected by education and our controls were more often in education and had completed more exams than the other groups (Chapter 2, Table 2.6.3) so this could be important. However, poorer educational attainment is suspected to be one result of the disease process and while the HR subjects do not have a schizophrenic illness it has been shown by Professor Hafner and colleagues (Hafner et al., 1998) that the process of

social decline may begin at least 5/6 years prior to the illness onset and so this explanation might account for some of the reduction in IQ scores in patients and among some members of the HR group, specifically those who will develop schizophrenia. However, this does not explain the findings of pervasive IQ deficits in patients in childhood (e.g. Offord and Cross, 1971; Jones et al., 1994). It indeed may explain some of the findings from the conscript studies (David et al., 1997). IQ deficits have been seen, not only in studies of pre-schizophrenia but also, and more relevantly, in studies of the offspring of patients with schizophrenia, although the confounding effect of social class could not be ruled out in many previous studies (Watt, 1984). An effect size of 0.39 was reported across HR studies comparing the offspring of patients with schizophrenia to the offspring of normal controls (Alyward, 1984). Reduced IQ was not specific to the offspring of patients with schizophrenia although it was most marked in these subjects (Asarnow, 1988; Alyward, 1984).

An increased rate of perinatal complications in the birth histories of HR subjects, but not controls, was found to correlate with a reduction in IQ (reported by Alyward, 1984). Perinatal complications are known to increase the risk for schizophrenia (e.g. Geddes et al., 1999) and hypoxic events have been specifically implicated (e.g. Zornberg et al., 1999) as risk factors, and are also known to lead to damage in the medial temporal areas of the brain, those areas often implicated in the pathogenesis of schizophrenia. Also perinatal complications were seen to interact with genetic risk, to increase the risk for schizophrenia (Cannon et al., 1993). While we cannot answer the possible role of this mechanism in the finding of reduced intellectual capacity in this HR group, perinatal data has been collected in the current sample and will provide a clearer picture at a later stage. Nonetheless, the IQ reduction in the high-risk group and the patients is a striking, if not unsurprising, finding. It has been estimated that between 10 and 15% of the HR group, will go on to develop schizophrenia, therefore the group is obviously a mixture of pre-schizophrenic subjects and subjects who will remain well, and probably those who are biologically unsusceptible (Garver, 1987). It is possible that those who will develop schizophrenia are causing a shift in the distribution and pulling the mean downwards. If the observed IQ reduction was only relevant to a subgroup, then greater variability of IQ scores would be expected in the HR group compared to the controls,

however this is not the case. It would therefore seem plausible that one expression of the genetic risk for schizophrenia is a reduction in IQ compared to normal controls, although at the same time, there is obviously considerable overlap in the distributions. This means that a subject could not be identified as 'at risk' purely on the basis of an IQ test score alone.

In both the Controls, and HR group, but not the Patients, PIQ was higher than VIQ, but not significantly so. This is contrary to other studies that have reported higher VIQ scores in such studies (Aylward et al., 1984). There was a significant difference between FSIQ and NART FSIQ for the patient group, indicating that the current performance of the group was on average 6 points lower than the estimate of pre-morbid functioning. This estimate of decline in function was not nearly as great as that reported by Frith et al. (1991), an average16 points, but the present sample is young and in the early stages of illness. It would be interesting to evaluate this group in 5 years time when the intellectual decline may be complete (Frith et al 1991; Dunkely and Rogers, 1994).

There is little doubt that the groups differ in terms of IQ. It is difficult to explain its occurrence except that it is not a new finding and may be one expression of the genetic risk/vulnerability for schizophrenia. What is certain is that this finding created much confusion about how to proceed with the analysis. It is known that IQ affects neuropsychological test results generally, so deficits in other areas could well be merely a reflection of the general deficit. Not to account for IQ would exaggerate differences between the groups and would not shed any light on possible differential deficits in other areas, as any differences could simply be due to the general deficit. Education and personal social class are known to be affected by the disease process and as the social class of origin was the same across groups, it was decided that the analyses should be conducted with NART estimated pre-morbid IQ as a co-variate. Although the reliability of the NART has been questioned (Heinrichs and Zakzanis, 1999), other studies have reported it to be highly reliable (Crawford et al., 1988; O'Carroll, 1987) and it appeared our best solution.

Without controlling for IQ significant differences were seen in patients compared to controls for all domains of function and comparing the controls and the HR group deficits were seen in all domains except mental control/encoding.

Controlling for NART, significant group differences remained in aspects of verbal learning and memory. The executive function deficit was seen in the HR group only, compared to Controls. The learning and memory deficit, and the visuo-spatial deficit, were characteristic of both the HR and Patient groups. This is a very intriguing finding, particularly as both executive function and memory deficits, were reported to be differentially compromised in patients with schizophrenia in addition to a general impairment (e.g. Elliot et al., 1998). Deficits in these domains of function were also reported in HR and family studies (see Kremen et al., 1994). Visuo-spatial deficits have been identified in patients with schizophrenia but do not appear to be particularly discriminating (Heinrichs and Zakzanis, 1998), and they have been less well studied in HR and family groups (Kremen et al., 1994). Patients gained fewer words on subsequent trials of the RAVLT compared to the other groups, and remembered less words, but not significantly less, in the delayed recall trial. This might suggest a deficit with encoding the information. It may also represent difficulties in storing information or retrieval. The difference between the number of words recalled on the recognition trial for list A (cued recall) and delayed recall trial (free recall), was significantly greater in the HR group compared to Controls and there was a trend for the same finding in the Patients. This might mean that the HR and Patient groups encode the material less efficiently or that strategies for remembering were not implemented in these groups so well as they were in controls. This could reflect poorer organisation of the material in memory and difficulty accessing the material under free recall conditions compared to cued recall. This indeed could reflect a deficit in working memory, and represent a difficulty with executive function. Unfortunately greater detail was not derived about the type of clustering/or semantic associations used by individuals to recall the material.

In terms of the CPT-IP, Patients had lower D prime values and made significantly more random errors in both distraction and speed conditions, controlling for NART the significance remained for D prime scores only.

No differences were found between the HR and control group in terms of the CPT-IP. This was somewhat surprising as deficits on this version of the test have been reported in HR samples (e.g. Cornblatt et al., 1989, 1992) and in adult relatives of patients with schizophrenia (Laurent et al., 1999; Franke et al., 1994) and in particular, reduced D prime values, were suggested to be risk indicator for the development of schizophrenia (Erlenmeyer-Kimling and Cornblatt, 1987). It could well be that there is a currently unidentifiable subgroup of HR subjects, who will later develop schizophrenia, and also have reduced D prime values, but are hidden within the overall group. Indeed there is some evidence of a relationship between symptoms in the HR group and reduced D prime values, and is outlined in Chapter 8.

One problem is that there is no clinical cut-off for the CPT-IP below which a response would be deemed as 'deviant'. Comparing the HR groups D prime values to such values reported for other samples, the HR group had similar D prime values to those quoted in Cornblatt et al. (1988) for normal families, and our controls had slightly higher values than their controls. Compared to data reported by Cornblatt et al. (1989) the HR group had slightly higher scores than the New York High Risk sample, but were less variable. These studies did not control for IQ. Cornblatt et al., (1988) did not find any effect of IQ on the CPT-IP in normal families and so, did not include it as a co-variate in further analyses. While we found IQ did not have any effect on log beta scores it did effect D prime and log randoms. A meta-analysis of the data would help greatly to clear up the confusion.

With so many statistical tests and variables, the possibility that the findings may be spurious was great so therefore multivariate analyses were carried out. While such methods are recommended in order to reduce the large number of data points to a more manageable scale, and to reduce type 1 errors, there is an obvious difficulty with such methods. Tests within a putative domain of function get combined into single scores but they may be very different and test different aspects of the function. However it is one solution to the problem. Two methods were used here, factor analyses and the method of standardised composite scores. The standardised composite score method

had the appeal of setting the test result to the same scale so that all tests can be easily compared. The results of the univariate analyses were broadly confirmed using multivariate techniques. Controlling for the general deficit (NART), in the factor analysis, the learning and memory factor scores were reduced in Patients compared to Controls and a trend remained for this finding in the HR group. Visuo-spatial performance was better in the controls than the HR group and attention/distractability (not CPT-IP) was compromised in the patients. The composite scores clearly showed deficits in the HR and patient group compared to controls for learning and memory and on the CPT-IP D prime scores were reduced in Patients and the HR group showed a significant increase in log randoms for the combined numbers conditions (Table 5.4). Given the lack of evidence for CPT-IP deficits in the HR group compared to controls in all of the univariate analyses, this may be a spurious finding. Learning and memory remain as areas of circumscribed deficits in the HR and patient groups.

Whether univariate or multivariate analyses are employed, the results appear to be very similar. The great benefit of the univariate approach is that there is greater detail available about the particular neuropsychological deficits observed.

The results of this study confirm those of other studies of this nature (HR studies and studies of the adult relatives of patients with schizophrenia, and studies of patients with schizophrenia), that there is a general deficit in intellectual functioning in the HR and Patient groups compared to the controls. In addition there appears to be circumscribed deficits, particularly in the domain of learning and memory, and possibly in aspects of executive function. In the Patients, selective attention may also be selectively compromised (as measured by the CPT-IP). There was no evidence that the HR group were poorer than controls on the CPT-IP, contrary to other studies.

These findings support the theories that implicate frontal and temporal lobe regions/ or connections between regions, to be deficient in schizophrenia and suggests that subjects at high genetic risk for schizophrenia exhibit similar but less marked deficits to those seen in the patients. The implications are that the vulnerability for schizophrenia is inherited and that one expression of this vulnerability is a broadly based

neuropsychological impairment. It is likely that the general reduction in IQ, and the specific deficits in learning and memory and executive functioning described here, represent a general vulnerability in many subjects rather than specific genetic markers in those few destined to develop schizophrenia in the future. This is supported by similar findings in other studies of adult relatives who have passed through a greater number of risk years, and are older than this group (see Kremen et al., 1994). However the CPT-IP deficits, seen here only in the Patient group, may well represent a specific marker for the later development of schizophrenia and so may be masked and not currently identifiable in the large, heterogeneous HR group.

CHAPTER SIX: NEUROPSYCHOLOGICAL FOLLOW-UP OF YOUNG PEOPLE AT HIGH GENETIC RISK FOR SCHIZOPHRENIA COMPARED TO CONTROLS

6.1. Introduction

This chapter is concerned with the degree, if any, to which the neuropsychological assessment results changed over time between assessments time one and time two. The particular aim was to determine if there were any differential changes among the groups. Only the high-risk (those without a diagnosis of schizophrenia) and controls subjects who were followed up are included in the analysis. This chapter does not include data on the first episode group.

6.2. Initial follow-up: First to second round assessment

The plan of the study was that each participant would be tested at 18 month intervals from recruitment until the end of the 5 year period of the study or until they developed a psychotic illness. By March 1999, when the study had been in operation for approximately 4 years, 80 high-risk subjects, and 22 controls had attended for a second round of assessments on average 2 years after the first assessment. A further 29 were eligible to attend but did not for various reasons, 10 agreed but did not show up on the day and a subsequent time could not be arranged, in addition 9 high-risk subjects agreed to take part a second time but were too busy when contacted. 5 subjects refused participation, 2 of whom decided at the 1st assessment that they would not take part on subsequent occasions. 22 controls returned, 11 more were eligible, 4 were lost to follow-up, 2 were pregnant and decided it was not a good time for them, and five were too busy but agreed in principle. (The subject numbers returning for follow-up assessments was outlined in chapter 2 but is restated here for continuity sake.) The neuropsychological assessment battery administered at time two is outlined in Table 3.2. Patients were only assessed at one time point. At the second assessment the AVLT proposed by Crawford and colleagues (1989) was employed to replace the RAVLT used in the first assessment, also a parallel version of the RBMT was administered, both were employed to reduce the problems of practice effects.

6.3.Statistical Analysis

Changes can be seen on repeated administration of neuropsychological assessments, even in the absence of any true change in neurobehavioural status, due to the less

than perfect reliability of the tests used, practice effects, changes in subjects motivation. These influences may vary between tests (Temkin et al., 1999). Regression towards the mean is a frequently observed phenomena observed when comparing scores at two testing times, where subjects who have extreme scores in either direction at one time point are likely to have scores closer to the mean of the group when tested again, although not always. The potential for problems arising from these phenomena was born in mind while conducting this analysis.

Statistical analyses were conducted using SPSS version 8.0 (SPSS, 1997). Repeated measures analysis of variance was conducted with group (high-risk or control) as a factor in the analysis. Gender was not included in the analysis as no gender by group interactions were noted in the baseline assessment and preliminary analyses showed that gender was not an important factor in our groups in the repeated assessment. The effect of time (measuring change between round one and round two assessments), and subject group represented the main effects in the analyses. Analyses were conducted with NART FSIQ as a co-variate, were appropriate. NART was not included as a co-variate in the analysis of WAIS-R FSIQ, VIQ, or PIQ, or for speed of comprehension or spot the word tests as they were too closely related. Time by NART and time by group interactions were assessed. The F values quoted are the Hotellings Trace Method values. Where the difference scores (between time one and time 2) were normally distributed, even if the original variable was not then the normal linear model was used. If however the difference scores were not normally distributed then the method suggested by Shirley (1981) was used, replacing the dependent variable and the co-variate, with the ranked values and then proceeding with the linear model. The results are presented in Table 6.1. The main aim was to find any effect of group, identifying any possible areas where the high-risk group performed more poorly over time than the controls.

Continuous Performance Test-Identical Pairs version

To measure the effect of distraction, a 2 group (high-risk versus control) by 2 distraction (distraction versus no distraction) x 2 stimulus (numbers versus shapes) by 2 assessments (first versus second) repeated measures analysis of co-variance was performed with NART as a co-variate. To measure the effect of speed a 2 group

(high-risk versus control) by 2 speed (fast versus slow) by 2 stimulus (numbers versus shapes) by 2 assessments (first versus second) repeated measures analysis of co-variance was performed with NART as a co-variate.

6.4. Neuropsychological differences between those who attended for follow-up and those who did not.

The demographic differences between those who returned for follow-up and those who did not are presented in Appendix 1 in Tables 2.6.14.1 to 2.6.14.10. The mean baseline NART (Nelson, 1982) for those high-risk participants who attended a second time and those who did not were 99.9 (sd 10.0) and 95.5 (sd 9.3) respectively ($t=1.70$, df 103, $p=0.10$). The mean NART scores for the control participants who attended for a second assessment and those who did not were 105.2 (8.1) and 104.3 (8.8) respectively ($t=0.30$, df 31, $p>0.05$). The mean WAIS-R FSIQ for the high-risk group who attended a second time was 100.2 (sd 13.7) and those who did not it was 93.7 (sd 9.6) ($t=2.70$, df 67.25, $p=0.01$). For the control group those who returned had an average WAIS-R FSIQ of 106.2 (sd 11.8) compared with 103.0 (sd 18.6) for those who did not return ($t=0.61$, df 31, $p>0.05$).

These results indicate that those of the HR group who did not attend for a second assessment but were eligible had lower IQs than those who did attend; such a trend was not evident in the controls. The true reason for the difference in IQs between the high-risk subjects who returned compared to those who did not is not known. It was noted that the less intellectually able of the HR group often found the neuropsychological assessment battery difficult and were often anxious to perform well on the tests in a way that the controls were not. The high-risk group were aware of their family history and worried often that poor performance on the tests might indicate something wrong with them. While every reassurance was given to the subjects, it is possible that this was a factor in their decision not to attend. Fourteen agreed in principle to return, 9 were too busy at the time and 5 did not show up to the appointment, performance anxiety may well have been a factor in their decision. Those who were uncontactable generally had more chaotic life styles, and they were

generally, more socially deprived (however not always), these factors are probably related to IQ in these subjects, although the real reasons are not known.

6.5. Results

The results of the analyses are presented in Table 6.1. Means are presented with standard deviations for univariate analyses and adjusted means and standard errors are presented for the multivariate analyses. Firstly the groups were compared in terms of current and premorbid IQ function. T-tests were conducted to search for differences between the HR and control group. There were no significant differences in terms of VIQ. The groups differed significantly in terms of PIQ, and FSIQ. The groups also differed significantly in terms of NART with the high-risk group having significantly lower average scores than the control group average. The groups also differed in terms of the Spot the word test (a similar test to the NART), however both groups improved on this test over time. Given the findings from the first round of assessments, NART was controlled in the analyses where appropriate.

Block design was repeated as a simple measure of current cognitive function and also as a measure of visuo-spatial ability. Both groups significantly improved on the test, likely due to practice effects to some degree. There remained a significant group difference in the expected direction (HR < Controls); controlling for pre-morbid function (NART) only a trend remained.

6.5.1.Executive function

There was significant improvement over time in both groups for the measures of the Stroop test, both for the incongruous condition and for the difference between the baseline condition and the incongruous condition. There was a significant time by NART interaction for these measures also. No significant time effects were noted for any other executive measure. There was a significant difference between the groups in terms of the number of 4 legged animals remembered, a measure of verbal (semantic) fluency. High-risk subjects recalled significantly less animal names than the controls; this difference was consistent over time. There was a significant group effect for total Hayling errors. The total number of errors dropped on average

between round 1 and 2 in both groups. The number of errors remained significantly higher in the high-risk group compared to the Controls. This group effect was present for both type A errors, the most deviant type, and type B errors.

6.5.2.Perceptual motor speed.

No group differences were identified on any measure of perceptual motor speed, controlling for NART. When digit symbol was analysed without controlling for NART a significant group effect was found, and significant improvement over time was noted for both groups. Trails A and B were introduced into the assessment battery at the second assessment point. Trails A and B were analysed using univariate analysis of covariance with NART as a co-variate. No significant group differences were noted.

6.5.3.Mental control encoding

Digit span forwards and digit span backwards were analysed, both with and without NART as a co-variate. The raw scores were analysed in both cases. No group differences were identified. There was no significant improvement over time in either group.

6.5.4.Verbal ability and language

The tests in this domain were the token test, the Speed of Comprehension test and the overall Speed and Capacity of Language Processing test (SCOLP; arguably a test of mental ability but placed in the verbal and language domain here). There was a significant improvement over time for the speed of comprehension test only, and a trend towards the controls performing better on this test than the high-risk subjects.

6.5.5.Learning and memory measures.

This domain was comprised of components of the Rey Auditory Verbal Learning Test (RAVLT) for assessment one and a parallel version of the RAVLT by Crawford (outlined in chapter 3) for the second assessment; list A recall, total recall, delayed recall, and recall of list B. Also the visual reproductions of the WMS-R immediate and delayed conditions, the Rivermead Behavioural Memory Test standardised scores and the story immediate and story delayed recall conditions.

No time effect was noted for any of the AVLT components. There was a significant time by group effect for trial one where the control group's performance was originally better than the HR group but at follow-up they performed slightly more poorly than the HR group, although not significantly so. There was a trend towards poorer performance in the high-risk group compared to controls for the delayed recall section of the AVLT. An analysis was conducted (not presented in the Tables) to assess if there was a group difference between the delayed recall of list A (free recall), and the number of words remembered on the recognition trial form list A (cued recall). A difference score was computed (recognition – delayed recall) and a significant group difference was noted between the groups ($F=5.03$; $p=0.03$) where the difference score for the controls (mean=1.72; s.e.=0.40) was significantly less than the difference in the HR group (mean=2.76; s.e.=0.21) although the number of words remember in the recognition trials was identical for both groups. There were no significant group differences for the recognition of list A or B. For recognition of trial A there was a group by time interaction showing that from time 1 to 2 the control groups average stayed the same while the HR group lost on average, one word. No group effects were noted for the visual reproduction sub-test, a significant effect was noted for the delayed recall section of this test with the control mean increasing over time.

Significant group effects were noted for both the story immediate recall and for the delayed story recall, with the high-risk group performing significantly more poorly on both. The difference between the standardised RBMT at time one and time two was not normally distributed for both the high-risk and controls. The analysis of co-variance was conducted on the ranked dependent and independent variables (Shirley, 1981). A trend toward overall poorer memory performance was observed in the high-risk group. There was a significant effect of time also, with RBMT standardised scores decreasing in both groups over time.

6.5.6.Summary

Significant group differences were found for baseline measures of current IQ pre-morbid intellectual function. There was a trend towards poorer performance by the high-risk group compared to controls for the delayed recall section of the AVLT. On tests of executive function the high-risk group performed significantly more poorly in terms of remembering the names of 4 legged animals. They also made significantly more errors on the Hayling Sentence Completion Test overall, and for both type A and B errors. There was a trend towards poorer performance on the speed of comprehension test. For the RBMT story immediate and delayed conditions, the HR group were significantly poorer than controls. There was a trend for the HR group to be perform more poorly on the RBMT overall compared to controls.

The high-risk group performed most poorly compared to controls, in the area of executive function and memory.

6.6. CPT-IP Results

The results of the CPT-IP analysis measuring the effect of distraction are displayed in Tables 6.2 and 6.4 (interactions are presented here) and the analysis measuring the effect of speed are given in Tables 6.3 and 6.5 (interactions are presented here).

6.6.1 Effect of Distraction

There were no significant changes in performance between the two rounds as can be seen from Table 6.4, also from Table 6.3 it can be seen that there were no significant main effect for stimulus, group or distraction. NART was a significant co-variate for both log randoms and d prime but not for log beta (the measure of response bias). It can be seen from Table 6.4 that there was a significant group by stimulus by assessment interaction for log randoms and for d'. The HR group's attentional capacity (d') improved for shapes (both in the distraction and non-distraction conditions) between the two assessments, while the Control group's attentional capacity improved more for numbers. There was a decrease in random responding (ln randoms) for the numbers conditions between the two assessments for the high-risk group while random responding (ln randoms) decreased more for the shapes

conditions between the two assessments in the control group. There was a differential change in the performance of the groups over time for the different stimuli (numbers and shapes).

6.6.2 Effect of speed

From Table 6.3 and Table 6.5 it can be seen that there were no significant main effect of group, stimulus, or speed for d', log beta, or ln randoms. There was a significant effect of the co-variate, NART, for both ln randoms, and for d', but not for log beta. Two significant interactions were noted. A significant group by stimulus by speed by assessment interaction was found for d'. Controls made improvements between round one and round 2 for numbers both fast and slow conditions. The high-risk group had an increase in scores for the fast numbers condition, but scores were reduced in the slow numbers condition. For shapes the high-risk group made greater improvements between rounds one and two for the fast conditions than controls, but less than the controls for slow shapes. A significant group by stimulus by speed interaction for log beta was found. The control group's scores were reduced in the slow compared to the fast condition for numbers (indicating less biased responding in the slow numbers condition), the opposite effect was observed for shapes. The high-risk group's scores increased more as speed reduced (i.e. from fast to slow conditions), indicating greater response bias in the slow condition for the HR group for both numbers and shapes.

The presence of interactions make interpretations very difficult and must be interpreted carefully and they have been interpreted here as they may hint at differences in performance styles among the groups, which are not marked enough to lead to significant group main effects or may obscure such differences.

Table 6.1. Neuropsychological variables compared across groups, initial univariate analysis.

	HIGH RISK, n=80 Mean (sd/se)	CONTROL, n=22 Mean (sd/se)	EFFECT OF TIME F	P	TIME *NART F	P	TIME*GROUP F	P	NART F	P	GROUP F	P
Current IQ												
Verbal IQ	98.69 (12.36)	103.41 (10.74)									1.63	0.11
Performance IQ	101.79 (14.66)	108.77 (14.65)									1.98	**0.05**
FSIQ	100.01 (13.65)	106.23 (11.82)									1.94	**0.05**
Block design 1	11.31 (0.35)	13.43 (0.64)	0.38	0.54	1.24	0.27	1.96	0.16	12.85	0.001	3.28	**0.07**
Block design 2	12.46 (0.36)	14.14 (0.66)	23.06	0.000			1.27	0.26			7.10	**0.009**
Premorbid IQ												
NART	99.71 (10.13)	105.18 (8.09)									2.32	**0.02**
NART-FSIQ	-0.39 (10.05)	-1.04 (10.38)									-0.27	0.79
Spot the Word 1	45.61 (0.58)	48.05 (1.12)										
Spot the Word 2	47.27 (0.52)	49.00 (0.99)	5.50	0.02			0.41	0.52			3.90	**0.05**
Executive function												
STROOP 3 (R1)	22.33 (0.55)	22.64 (1.02)										
STROOP 3 (R2)	21.15 (0.47)	20.63 (0.88)	6.92	0.01	5.05	0.03	1.03	0.31	29.18	0.00	0.01	0.93
STROOP 1-3 (1)	12.35 (0.54)	12.30 (1.00)										
STROOP 1-3 (2)	11.44 (0.45)	10.44 (0.83)	7.32	0.008	5.96	0.02	1.00	0.32	20.99	0.00	0.31	0.58
FAS (R1)	39.96 (1.32)	39.96 (1.32)										
FAS (R2)	41.04 (1.42)	42.35 (2.70)	0.69	0.41	1.16	0.28	0.94	0.33	34.93	0.00	0.02	0.58
Animals (R1)	15.79 (0.67)	18.14 (1.29)										
Animals (R2)	15.69 (0.55)	18.27 (1.07)	0.57	0.81	0.06	0.81	0.04	0.85	10.20	0.002	4.21	**0.04**
Ln HSCT timeA1	16.79 (15.15, 18.67)	15.03 (12.48, 18.35)										
Ln HSCT timeA2	14.24 (13.07, 15.57)	12.45 (10.70, 14.67)	0.92	0.34	0.39	0.54	0.08	0.78	9.68	0.002	2.04	0.16
Ln HSCT timeB1	31.46 (26.85, 37.14)	24.29 (18.45, 32.80)										
Ln HSCT timeB2	23.90 (20.60, 27.94)	21.63 (16.51, 29.18)	0.47	0.49	0.17	0.68	0.92	0.34	2.01	0.16	1.41	0.24
Ln HSCT B-A 1	22.11 (3.26)	14.95 (6.24)										
Ln HSCT B-A 1	15.72 (2.59)	17.69 (4.95)	0.11	0.74	0.16	0.69	2.35	0.13	0.06	0.80	0.21	0.65
HSCT errors 1	9.41 (0.15)	3.48 (2.22)										
HSCT errors 2	4.28 (0.69)	2.47 (1.33)	0.03	0.86	0.23	0.63	2.95	0.09	0.005	0.95	5.09	**0.03**
HSCT errors A 1	4.13 (0.56)	2.28 (1.08)										
HSCT errors A 2	1.75 (0.31)	1.24 (0.60)	39.88	0.00	0.35	0.56	1.40	0.24	0.12	0.73	4.72	**0.03**
HSCT errors B 1	5.28 (0.79)	1.19 (1.53)										
HSCT errors B 2	2.53 (0.47)	1.23 (0.90)	0.04	0.85	0.00	0.98	2.45	0.12	0.04	0.84	5.75	**0.02**

	HIGH RISK, n=80 Mean (sd/se)	CONTROL, n=22 Mean (sd/se)	Effect of time		TIME *NART		TIME*GROUP		NART		GROUP	
			F	P	F	P	F	P	F	P	F	P
Perceptual motor speed												
Digit Symbol 1	10.62 (0.33)	11.90 (0.65)	0.07	0.80	0.005	0.94	0.64	0.42	12.66	0.001	1.79	0.18
Digit Symbol 2	11.13 (0.32)	12.80 (0.62)	9.62	0.003			0.72	0.40			4.74	**0.03**
Trails A	28.57 (1.00)	21.74 (2.29)							0.38	0.54	2.24	0.14
Trails B	57.25 (2.12)	52.10 (4.85)							7.43	0.01	0.66	0.44
Trails A-B	28.68 (2.00)	30.36 (4.58)							6.66	0.01	0.01	0.94
Mental control /encoding												
Digits forward 1	9.02 (0.23)	8.12 (0.44)	2.27	0.14	1.97	0.16	2.46	0.12	22.07	0.00	0.97	0.33
Digits forward 2	8.92 (0.28)	8.84 (0.53)	1.19	0.28			1.43	0.23			0.10	0.76
Digit backward 1	7.28 (0.26)	7.51 (0.50)	0.03	0.87	0.04	0.84	0.49	0.48	16.74	0.00	0.005	0.95
Digit backward 2	7.56 (0.26)	7.39 (0.49)	0.08	0.77			0.41	0.52			1.25	0.27
Verbal ability and language												
Token Test 1	162.09 (0.18)	162.08 (0.34)										
Token Test 2	162.40 (0.13)	162.48 (0.26)	3.02	0.09	2.41	0.12	0.06	0.80	15.58	0.00	0.01	0.91
Speed of comp. 1	11.71 (0.71)	12.03 (0.62)	0.03	0.86	0.82	0.78	0.02	0.87	61.70	0.00	0.33	0.57
Speed of comp. 2	12.85 (0.32)	13.26 (0.63)	17.86	0.00			0.02	0.88			4.58	**0.03**
SCOLP (R1)	-1.73 (0.38)	-1.97 (0.76)										
SCOLP (R2)	-1.76 (0.38)	-2.65 (0.76)	0.42	0.52	0.33	0.57	0.54	0.47	1.16	0.28	0.58	0.45
Learning and memory												
RAVLT I (R1)	6.76 (0.22)	7.37 (0.43)										
AVLT 1 (R2)	5.85 (0.20)	5.37 (0.38)	0.07	0.79	0.81	0.37	4.35	0.04	6.62	0.01	0.03	0.85
RAVLT total I-V (1)	52.72 (0.98)	54.73 (1.88)										
AVLT total I-V (2)	49.49 (0.86)	49.42 (1.65)	0.11	0.74	0.03	0.86	1.20	0.28	19.00	0.00	0.29	0.89
RAVLT Delayed recall (1)	10.70 (0.311)	12.06 (0.59)										
AVLT Delayed recall (2)	9.75 (0.30)	10.59 (0.58)	0.97	0.33	0.37	0.54	0.56	0.46	7.51	0.007	3.61	**0.06**
RAVLT list B(1)	6.31 (0.21)	6.54 (0.40)										
AVLT list B(2)	6.34 (0.23)	6.38 (0.44)	0.39	0.54	0.44	0.51	0.11	0.74	8.66	0.004	0.13	0.72
RAVLT Recognition A 1	13.33 (0.26)	12.90 (0.49)										

	HIGH RISK, n=80 Mean (sd/se)	CONTROL, n=22 Mean (sd/se)	Effect Of Time		TIME *NART		TIME*GROUP		NART		GROUP	
			F	P	F	P	F	P	F	P	F	P
AVLT Recognition A 2	12.60 (0.27)	13.19 (0.51)	0.14	0.71	0.23	0.63	3.80	0.05	4.49	0.04	0.02	0.88
RAVLT Recognition B 1	7.19 (0.31)	7.1 (0.59)										
AVLT Recognition B 2	6.30 (0.33)	6.61 (0.62)	1.78	0.18	2.55	0.14	0.33	0.57	3.18	0.08	0.03	0.86
Visual Reprod. Immediate 1	36.15 (0.43)	36.53 (0.85)										
Visual Reprod. Immediate 2	35.48 (0.39)	35.88 (0.85)	0.56	0.81	0.18	0.67	0.00	0.98	21.86	0.00	0.22	0.64
Visual Reprod. Delayed 1	33.75 (0.58)	33.84 (1.16)										
Visual Reprod. Delayed 2	33.65 (0.51)	34.30 (1.02)	4.59	0.03	4.68	0.03	0.21	0.65	23.63	0.00	0.12	0.73
RBMT story immediate 1	9.86 (0.33)	11.29 (0.64)										
RBMT story immediate 2	9.20 (0.39)	10.47 (0.75)	0.32	0.57	0.14	0.71	0.04	0.84	31.25	0.00	3.99	**0.05**
RBMT story delayed 1	8.72 (0.33)	10.19 (0.63)										
RBMT story delayed 2	8.16 (0.37)	10.33 (0.70)	0.04	0.85	0.02	0.89	0.77	0.38	27.18	0.00	7.94	**0.006**
RBMT standard. Score 1	22.5(21, 24)	24 (22, 24)										
RBMT standard. Score 2	22 (20, 24)	23 (21.5, 24)	21.60	0.00	0.26	0.61	1.25	0.27	6.23	0.01	3.40	**0.07**

Table 6.2. CPT –IP Adjusted means presented (see Table 6.4 for interactions)

		High Risk n=59 Mean (se)	Control n=19 Mean (se)	Group F	P	Stimulus F	P	NART F	P	Distraction F	P
Log Randoms											
Fast Numbers	No distraction R1	0.43 (0.07)	0.22 (0.13)								
	No distraction R2	0.26 (0.07)	0.15 (0.13)								
	Distraction R1	0.63 (0.07)	0.46 (0.14)								
Fast Shapes	Distraction R2	0.43 (0.08)	0.39 (0.16)	1.16	0.28	0.01	0.98	12.46	0.001	2.23	0.14
	No distraction R1	0.46 (0.07)	0.33 (0.14)								
	No distraction R2	0.35 (0.08)	0.23 (0.15)								
	Distraction R1	0.48 (0.08)	0.56 (0.15)								
	Distraction R2	0.44 (0.08)	0.19 (0.14)								
D Prime											
Fast Numbers	No distraction R1	1.93 (0.11)	1.66 (0.19)								
	No distraction R2	2.14 (0.11)	2.25 (0.20)								
	Distraction R1	1.73 (0.11)	1.58 (0.19)	0.004	0.95	0.24	0.63	21.94	0.00	0.42	0.52
Fast Shapes	Distraction R2	1.82 (0.10)	1.73 (0.19)								
	No distraction R1	1.80 (0.07)	1.85 (0.14)								
	No distraction R2	2.25 (0.11)	2.24 (0.18)								
	Distraction R1	1.98 (0.11)	2.29 (0.20)								
	Distraction R2	2.43 (0.11)	2.41 (0.20)								
Log Beta											
Fast Numbers	No distraction R1	-0.32 (0.10)	-0.31 (0.18)								
	No distraction R2	-0.12 (0.12)	-0.28 (0.21)								
	Distraction R1	-0.07 (0.09)	-0.14 (0.17)								
Fast Shapes	Distraction R2	-0.01 (0.09)	0.07 (0.16)								
	No distraction R1	-0.31 (0.09)	-0.08 (0.18)	0.02	0.88	3.77	0.06	0.22	0.64	0.59	0.45
	No distraction R2	-0.18 (0.11)	0.23 (0.20)								
	Distraction R1	-0.23 (0.12)	-0.39 (0.22)								
	Distraction R2	-0.08 (0.12)	-0.11 (0.22)								

Table 6.3 CPT –IP Adjusted means presented (see Table 6.5 for interactions)

		High Risk n=59 Mean (se)	Control n=19 Mean (se)	Group F	P	Stimulus F	P	NART F	P	Speed F	P
Log Randoms											
Numbers	Fast R1	0.43 (0.07)	0.22 (0.13)								
No distraction	Fast R2	0.26 (0.07)	0.15 (0.13)								
	Slow R1	0.39 (0.07)	0.17 (0.12)								
Shapes	Slow R2	0.26 (0.06)	0.19 (0.10)								
No distraction	Fast R1	0.46 (0.07)	0.33 (0.14)	1.39	0.24	1.97	0.16	14.87	0.00	2.61	0.11
	Fast R2	0.35 (0.08)	0.23 (0.14)								
	Slow R1	0.50 (0.08)	0.34 (0.14)								
	Slow R2	0.36 (0.08)	0.35 (0.15)								
D Prime											
Fast Numbers	Fast R1	1.93(0.11)	1.62 (0.19)								
	Fast R2	2.14 (0.11)	2.26 (0.20)								
	Slow R1	2.37 (0.12)	2.21 (0.23)								
	Slow R2	2.35 (0.11)	2.32 (0.21)								
Fast Shapes	Fast R1	1.80 (0.07)	1.87 (0.13)	0.02	0.89	1.18	0.28	22.88	0.00	0.43	0.51
	Fast R2	2.25 (0.10)	2.24 (0.18)								
	Slow R1	2.40 (0.11)	2.57 (0.20)								
	Slow R2	2.62 (0.10)	2.92 (0.19)								
Log Beta											
Fast Numbers	Fast R1	-0.31 (0.10)	-0.24 (0.18)								
	Fast R2	-0.13 (0.12)	-0.28 (0.21)								
	Slow R1	-0.15 (0.11)	-0.35 (0.20)								
	Slow R2	-0.33 (0.12)	0.17 (0.22)								
Fast Shapes	Fast R1	-0.31 (0.95)	-0.04 (0.17)	0.13	0.71	2.76	0.10	0.42	0.52	2.03	0.16
	Fast R2	-0.02 (0.11)	0.27 (0.20)								
	Slow R1	-0.24 (0.12)	-0.48 (0.23)								
	Slow R2	-0.15 (0.13)	-0.09 (0.24)								

Table 6.4. Summary of F values from repeated measures ANOVAs for the outcome measures of the CPT-IP (d', ln beta, and ln randoms) for the high-risk and control groups; distraction versus no distraction

	Attentional capacity d'	Response bias Ln beta	Random responses Ln randoms
Assessment (first versus second)	1.63	0.58	0.16
Group x Stimulus	0.89	0.61	0.16
Group x Distraction	0.18	1.30	0.30
Group x Assessment	0.01	0.08	0.01
Group x Stimulus x Distraction	0.97	3.29	0.10
Group x Stimulus x Assessment	4.77*	0.29	5.32*
Group x Distraction x Assessment	3.07	0.66	0.91
Group x Stimulus x Distraction x Assessment	0.08	0.41	1.24

* $p<0.05$

Table 6.5. Summary of F values from repeated measures ANOVAs for the outcome measures of the CPT-IP (d', ln beta, and ln randoms) for the high-risk and control groups; fast versus slow

	Attentional capacity d'	Response bias Ln beta	Random responses Ln randoms
Assessment (first versus second)	1.46	0.08	0.50
Group x Stimulus	0.68	0.22	0.30
Group x Speed	1.45	0.20	0.32
Group x Assessment	1.44	2.02	0.97
Group x Stimulus x Speed	0.73	4.57*	0.01
Group x Stimulus x Assessment	0.55	0.29	0.20
Group x Speed x Assessment	0.39	6.29	0.28
Group x Stimulus x Speed x Assessment	4.83*	2.91	0.22

* $p<0.05$

6.7. Follow up assessments: assessments 1,2 and 3

Methodology

The Neuropsychological assessment battery administered to those who returned for a third round of assessments is outlined in Table 3.3. A total of 29 high-risk subjects and 4 controls returned for a third round of assessments. Repeated measures analysis

of variance was conducted with NART as a co-variate where appropriate. The number of controls was small and the analyses of variance may not be accurate due to the small number, however, there are 3 observations per person. This is really a preliminary analysis to look at any changes over time, both within and across the groups, and to see if these changes are differential. ***(It must be remembered that the number of subjects (n=29 high risk and n=4 controls) returning for the 3rd round is very small compared to the overall number, however the advantage is that it is a within person comparison and may be valuable in order to identify any changes in test behaviour over time, whether a property of the test or of the individual performing them.)***

T-tests were conducted and no differences were observed between the groups for any of the IQ variables as measured at baseline (Verbal IQ (VIQ), Performance IQ (PIQ), Full Scale IQ (FSIQ), or NART). Both t and p values are presented in Table 6.6 under the heading 'Group' and are displayed in bold italics. Also there was no significant NART - FSIQ difference between the groups. There was a trend towards less animal names being remembered by the high-risk group compared to the controls. NART was included as a co-variate in the analyses even though there were no significant differences between the groups in terms of NART, but because of the importance of NART in the other analyses, both at baseline and initial follow-up. There were significant improvements over time for the digit symbol test. Trails A and B were administered for the first time at round 2 and were repeated at the 3rd assessment. Significant improvements were noted for performance on Trails A and there was a trend toward improved performance over time for Trails B. A time x group interaction was noted for the story, delayed recall condition, where for the control group the mean number of ideas remembered from story 3 (mean=6.81) dropped dramatically from the mean at round two assessment (mean=12.05). The HR subjects did not show this trend. Significant effects of the co-variate, NART, were observed for all Stroop measures, digits forwards, digits backwards, story immediate recall, story delayed recall, RBMT standardised scores, and for Trails B and Trails A-B. No other significant effects or trends were noted in these data. These data are largely descriptive, they were presented to allow the profiles of any

changes across time in the subjects to be viewed, but it only includes a small proportion of the original sample.

Table 6.6. Neuropsychological variables compared across groups, initial univariate analysis; rounds 1 to 3

	HIGH RISK, N=29 Mean (se)	CONTROL, N=4 Mean (se)	EFFECT OF TIME F	P	TIME *NART F	P	TIME*GROUP F	P	NART F	P	GROUP F	P
Current IQ											*t*	*p*
Verbal IQ	98.33 (12.70)	107.75 (7.67)									***1.43***	***0.16***
Performance IQ	102.00 (14.16)	111.75 (9.74)									***1.32***	***0.20***
Full Scale IQ	99.74 (13.35)	110.75 (9.11)									***1.58***	***0.12***
Block Design 1	11.88 (0.58)	14.75 (1.46)										
Block Design 2	13.20 (0.61)	15.25 (1.52)										
Block Design 3	13.20 (0.62)	14.50 (1.54)	1.71	0.19			1.20	0.29			1.86	0.18
Premorbid IQ												
NART	100.37(9.56)	108.00 (2.00)									***1.57***	***0.13***
NART-FSIQ	0.63 (10.96)	-2.75 (7.72)									***-0.59***	***0.56***
Executive function												
STROOP 3 (R1)	22.54 (1.09)	25.13 (2.79)										
STROOP 3 (R2)	20.84 (0.88)	22.49 (2.25)										
STROOP 3 (R3)	21.07 (0.76)	18.51 (1.95)	2.86	0.07	2.18	0.12	2.19	0.12	7.98	0.009	0.07	0.79
STROOP 1-3 (1)	10.77 (0.46)	10.73 (1.21)										
STROOP 1-3 (2)	12.24 (0.53)	12.44 (1.39)										
STROOP 1-3 (3)	12.33 (0.48)	12.09 (1.27)	0.40	0.67	0.20	0.82	1.00	0.91	27.68	0.00	0.00	0.98
FAS (R1)	38.64 (2.24)	37.34 (5.90)										
FAS (R2)	41.42 (2.40)	43.74 (6.31)										
FAS (R3)	42.44 (2.05)	45.91 (5.39)	0.99	0.38	0.57	0.57	1.18	0.31	3.48	0.07	0.06	0.81
Animals (R1)	15.30 (1.08)	21.21 (2.88)										
Animals (R2)	15.31 (0.96)	19.89 (2.57)										
Animals (R3)	16.12 (0.88)	18.68 (2.36)	0.56	0.57	0.52	0.59	1.09	0.34	3.11	0.09	3.07	0.09
Ln HSCT timeA1	18.62 (14.43, 24.60)	18.08 (9.66, 40.10)										
Ln HSCT timeA2	14.17 (12.17, 16.60)	12.64 (8.76, 19.46)										
Ln HSCT timeA3	13.07 (11.61, 14.75)	12.87 (9.53, 18.080	2.41	0.10	1.71	0.19	0.11	0.89	1.72	0.20	0.06	0.81
Ln HSCT timeB1	36.08 (26.41, 50.58)	17.22 (9.34, 37.54)										
Ln HSCT timeB2	22.94 (17.82, 30.29)	16.79 (9.51, 34.33)										
Ln HSCT timeB3	21.17 (17.47, 26.07)	15.92 (10.21, 27.03)	1.29	0.28	1.02	0.36	0.85	0.34	0.44	0.51	2.44	0.13
Ln HSCT B-A 1	24.79 (6.68)	-3.19 (17.89)										
Ln HSCT B-A 2	16.02 (3.86)	1.75 (10.35)										
Ln HSCT B-A 3	11.46 (2.49)	3.19 (6.66)	0.02	0.98	0.02	0.98	1.00	0.37	2.48	0.13	1.26	0.27
HSCT errors 1	10.31 (2.30)	0.89 (6.17)										

	HIGH RISK, N=27 Mean (se)	CONTROL, N=4 Mean (se)	TIME F	P	TIME *NART F	P	TIME*GROUP F	P	NART F	P	GROUP F	P
HSCT errors 2	4.42 (1.29)	3.17 (3.46)										
HSCT errors 3	1.70 (0.63)	1.27 (1.680	0.13	0.88	0.17	0.85	1.61	0.21	1.34	0.26	0.08	0.78
HSCT errors A1	3.55 (0.80)	0.02 (2.14)										
HSCT errors A2	1.76 (0.66)	2.37 (1.77)										
HSCT errors A3	0.56 (0.27)	0.05 (0.72)	0.91	0.41	1.13	0.33	2.21	0.12	0.84	0.37	0.76	0.39
HSCT errors B1	6.76 (1.67)	0.87 (4.47)										
HSCT errors B2	2.09 (0.63)	0.33 (1.69)										
HSCT errors B3	1.24 (0.35)	0.12 (0.93)	0.28	0.76	0.17	0.84	0.87	0.42	0.07	0.79	2.06	0.16
Perceptual motor speed												
Digit Symbol 1	10.93 (0.650	12.00 (1.70)										
Digit Symbol 2	11.30 (0.52)	12.75 (1.36)										
Digit Symbol 3	12.07 (0.55)	14.25 (1.43)	5.40	0.01			0.56	0.57			1.10	0.30
Mental control /encoding												
Digits forwards 1	9.02 (0.38)	8.59 (1.02)										
Digits forwards 2	8.85 (0.45)	7.51 (1.20)										
Digits forwards 3	9.45 (0.41)	721 (1.09)	0.12	0.88	0.24	0.79	1.58	0.22	4.93	0.03	1.66	0.21
Digits backwards 1	7.08 (0.43)	6.72 (1.14)										
Digits backwards 2	7.15 (0.44)	6.97 (1.18)										
Digits backwards 3	7.58 (0.47)	8.61 (1.25)	0.46	0.63	0.45	0.64	0.97	0.38	5.72	0.02	0.02	0.88
Verbal ability and language												
Speed of comp 1	10.77 (0.46)	10.73 (1.21)										
Speed of comp 2	12.24 (0.53)	12.44 (1.39)										
Speed of comp 3	12.33 (0.48)	12.09 (1.27)	3.28	0.05			0.07	0.93			1.36	0.25
Learning and memory												
RAVLT I (R1)	6.44 (0.32)	7.55 (0.85)										
RAVLT 1 (R2)	5.66 (0.32)	5.31 (0.85)										
RAVLT 1 (R3)	6.29 (0.29)	7.26 (0.79)	0.05	0.95	0.02	0.98	1.20	0.31	1.64	0.21	0.75	0.39
RAVLT total (1)	51.43 (1.69)	55.09 (4.51)										
RAVLT total (2)	49.05 (1.40)	49.63 (3.76)										
RAVLT total (3)	50397 (1.12)	59.21 (3.01)	1.98	0.15	1.77	0.18	1.78	0.18	2.42	0.13	1.54	0.23
RAVLT Delayed recall (1)	10.14 (0.59)	11.80 (1.58)										
RAVLT DEL (2)	9.25 (0.50)	9.53 (1.33)										

	HIGH RISK, N=27 Mean (se)	CONTROL, N=4 Mean (se)	EFFECT OF TIME		TIME *NART		TIME*GROUP		NART		GROUP	
			F	P	F	P	F	P	F	P	F	P
RAVLT DEL (3)	10.40 (0.48)	12.04 (1.28)	0.54	0.59	0.32	0.72	0.56	0.57	1.57	0.22	0.93	0.34
RAVLT list B (1)	5.80 (0.30)	7.33 (0.80)										
RAVLT list B (2)	5.67 (0.33)	5.98 (0.88)										
RAVLT list B (3)	6.47 (0.32)	6.08 (0.85)	1.55	0.22	1.34	0.27	1.84	0.17	0.48	0.49	2.81	0.10
RBMT Story Immediate 1	9.67 (0.60)	10.95 (1.61)										
Story Immediate 2	8.76 (0.66)	12.39 (1.78)										
Story Immediate 3	8.62 (0.54)	9.33 (1.44)	0.22	0.80	0.24	0.79	1.24	0.30	9.43	0.005	2.02	0.17
RBMT Story Delayed 1	8.29 (0.58)	8.81 (1.56)										
Story Delayed 2	7.73 (0.59)	12.05 (1.57)										
Story Delayed 3	7.06 (0.54)	6.81 (1.44)	0.87	0.42	0.63	0.54	3.71	0.03	11.77	0.002	1.43	0.24
RBMT total standardised score1	21.76 (0.40)	22.13 (1.08)										
RBMT stand. 2	22.08 (0.420	21.22 (1.11)										
RBMT stand. 3	21.31 (0.420	21.68 (1.12)	0.97	0.39	1.16	0.32	0.45	0.64	8.34	0.007	0.002	0.96
Trails A2	29.10 (1.820	22.37 (4.88)										
Trails A3	25.91 (1.19)	18.97 (3.19)	8.41	0.007	7.73	0.01	0.003	0.96	2.32	0.14	2.95	0.10
Trails B2	60.02 (3.14)	52.21 (8.23)										
Trails B2	58.21 (3.57)	44.65 (9.36)	3.24	0.08	2.89	0.10	0.56	0.46	7.79	0.01	1.51	0.23
Trails A-B1	30.59 (3.03)	29.78 (7.96)										
Trails A-B2	31.97 (2.98)	25.57 (7.83)	0.06	0.80	0.05	0.82	0.37	0.55	6.08	0.02	0.25	0.62

There was a significant NART by time interaction for Trails A

6.8. DISCUSSION

The findings from these analyses are striking, and have served to confirm and strengthen the findings in Chapter 5. With only two groups being compared, the differences between the HR and Control groups have become very clear.

No differences between the groups were found for VIQ but differences in other aspects of IQ were found. A significant effect of time was apparent for a number of variables and was typified generally by a reduction in speed on timed tasks, and an increase in accuracy, which most likely reflect practice effects. The AVLT parallel version (Crawford et al., 1989) appears to have been a little more difficult than the original RAVLT with less words remembered in trial 1 and on the total trials although no significant effect of time was noted. For the HSCT, section B, the HR group had a greater reduction in time taken to complete the section compared to controls but it did not reach statistical significance. Only one time by group interaction was observed, for RAVLT trial one, where initially the Controls scored higher than the HR group but on the parallel version they scored slightly lower (although the actual difference was not significant), and may well represent regression to the mean.

Controlling for NART, group differences were found for semantic category of verbal fluency, 'animals', HSCT total errors, HSCT errors A, HSCT errors B, and delayed recall of the RAVLT, RBMT story immediate and delayed recall and a trend towards a difference on total RBMT standardised scores and block design. These findings are consistent with the first assessment and confirm continuing deficits in learning and memory, executive function and possibly visuo-spatial ability in the HR group compared to controls in addition to generally reduced IQ.

No group main effects were found for the CPT-IP, but some significant interactions were noted. The high-risk group was found to improve more over the two assessments (showing an improvement in attentional capacity as indicated by greater D prime scores, and they also made fewer random errors) with the spatial stimuli

(shapes) compared to the verbal stimuli (numbers), while the controls showed greater improvement on the verbal rather than the spatial stimuli (Table 6.2). This does not support the finding of Franke et al., (1994), who found the HR group to be equally poor at visual and verbal stimuli. However, Laurent et al., (1999) found relatives to have significantly lower D prime values for shapes.

Cornblatt et al., (1988) reported that a normal adolescent group appeared to process the spatial stimuli of the CPT-IP more accurately than they did verbal stimuli but they also appeared to be superior to normal adults in their spatial skills, while adults processed both types similarly. The authors concluded that spatial and verbal processing skills develop independently and may have differential rates of change. Spatial skills are superior to verbal skills throughout childhood and well into the teens and then start to decline somewhat in adulthood, while verbal skills peak much later. So the finding of differential improvement for shapes and numbers in the groups could represent a delay in normal cerebral development in the HR group relative to the controls, suggesting a more immature pattern of response. It has been reported that the numbers and shapes conditions of the CPT-IP involve different brain functions. Keilp et al., (1997) conducted a SPECT scan study of normal subjects conducting the CPT-IP. During the numbers task, left-sided activity was increased on multiple transverse slices in an anterior subcortical region that incorporated the anterior cingulate, frontal white matter, and much of the basal ganglia. Left-sided activity was also increased in a posterior subcortical region including the left side of the thalamus. They authors found relative perfusion to occipital regions, bilaterally, to be more extensive during the shapes task. Perhaps some deficits in the cortical connections supporting the execution of the numbers task, has prevented improvement of the verbal stimuli over time in the HR group, indeed the areas implicated in the execution of this aspect of the task are those reported to be deficit in schizophrenia. However, it should be noted that there is no recognised benchmark for the amount of change in CPT performance that would be deemed clinically relevant (Finkelstein et al., 1997). In the HR subjects reported here, bi-lateral structural abnormalities were observed at baseline (Lawrie et al., 1999), but were found to progress significantly only in the left amygdalo-

hippocampal complex and temporal lobe (Lawrie et al., 2000 in preparation). The relative lack of evidence supporting right hemisphere impairment suggests that spatial skills, localised in the right side are less affected by a delay, or abnormal, cerebral development.

The findings of deficits on the HSCT in the HR group confirm the findings of the baseline assessment and those previously reported on the first 100 subjects (Byrne et al., 1999). While there was a considerable reduction in errors over time in the HR group, the group differences remained a robust finding. The HR group remembered significantly fewer names of 'four legged animals', a verbal fluency task in the executive function domain. A trend remained for lower scores on the block design test for the HR group compared to controls, after controlling for NART. In the domain of learning and memory a trend for lower RAVLT delayed recall scores was observed in the HR group, significantly lower scores in the HR group were observed on the RBMT story immediate, and story delayed conditions and a trend for a reduction in RBMT standardised scores in the HR group remained. Group differences were observed on the speed of comprehension test, block design, and digit symbol tests without controlling for NART. The unadjusted analyses was conducted for these tests as they are highly related to overall measures of IQ and it may not make sense to control for IQ in analyses in which they are involved. It is interesting that the verbal fluency semantic category 'animals', the speed of comprehension test, and the digit symbol subtest, were found together, to load highly on the same factor in a factor analysis (factor 5, presented in Chapter 5, Table 5.7a). This factor was interpreted as indicating attention/ distractibility. Both deficits in remembering the names of animals and on the speed of comprehension test may suggests deficits in semantic memory consistent with studies in patients with schizophrenia (Tamlyn et al., 1992). A deficit in motor speed could be implicated in the case of Speed of Comprehension, digit symbol substitution, and block design, as all are timed tests requiring successful motor responses for their completion and a deficit of motor slowness could be the underlying difficulty, and has indeed been found in patients with schizophrenia (Nelson et al., 1990). It was suggested that this might represent impairment in the basal ganglia and medial systems involving the

lateral motor systems (Frith, 1995). Animals, block design, speed of comprehension and digit symbol, are all timed tasks, and so another explanation is that reduced scores on these tests may indicate general cognitive slowing.

There was a trend for the HR group to have lower AVLT delayed recall scores compared to the controls, this might mean that there was a greater loss of information over time in the HR group, suggesting a difficulty with the long term storage of information. However when given a 50 word list to identify the words from list A, the groups remembered similar numbers of words. In the baseline analysis it was also shown that compared to the delayed recall condition (free recall), the HR group recognised significantly more words than the other groups on the recognition trial (cued recall). It would appear that the difficulty is not the encoding of fewer words, but perhaps with free recall retrieval of information, possibly mediated by poor organisation of the words in memory and maybe due to the reduced usage of strategies in encoding. This could be representative of executive function difficulty.

The findings fit very well with the results of previous studies implicating a general intellectual deficit with pronounced specific impairments in memory and executive functioning and support the findings of Chapter 5. Also subtle motor slowness may be the underlying mechanism causing group differences in terms of speed of comprehension, digit symbol, and block design, however these findings were not strongly upheld once NART was controlled in the analyses. We did not find deficits of visual memory (supported by Goldberg et al., 1990). The trails test was introduced for the first time at round 2. Significant group differences did not appear on the trails making test, although the HR group were on average slower, but not significantly slower, in both conditions compared to the controls after NART was controlled. This is contrary to other studies that found deficits on this test in HR groups, particularly on trails B (outlined by Kremen et al., 1994).

The differences in both delayed and immediate recall on the RBMT story and the overall RBMT standardised scores are important. There was no difference between the groups in the amount of information lost between the immediate and delayed

recall conditions of the RBMT story. This could suggest that the HR group have consolidated less information, due to a difficulty with encoding, however it could be a difficulty with the free recall, unstructured recall, and if given a cue to recall the information the groups may have been equal in performance, as seen on the AVLT. This cannot be answered here, as there was no cued recall condition for the RBMT story. It is possible that the difference between the groups in terms of the overall RBMT score may reflect the difficulty with the story recall as the other items on the test proved to be relatively unchallenging to the non-patient groups, but were not analysed separately.

An obvious problem with this kind of research, and one that has been much commented on, is that task difficulties are not equated and different findings may simply represent the fact that some tests are more difficult than others. The upshot of this is that where differences are found, they are likely to exist and where they are not, it may be that given a more difficult version of the task, genuine differences might appear.

In the absence of functional imaging data for these groups, it is difficult to speculate about the underlying mechanisms of the observed dysfunctions. However it is likely that the underlying deficits would be the same as those found by others groups in patients with schizophrenia, and probably involve prefrontal-temporal dysconnectivity (e.g. Dolan et al., 1999). Soon, the groups in the present study will undergo functional MR imaging, and at that time the underlying mechanisms of the deficits in the HR group should become clearer. The evidence is continuing to accumulate that the classical lesion model based on the notion of a segregated neuropsychological deficit mapping to a structural brain lesion is unlikely to be appropriate to explain the complex pattern of behaviours seen in schizophrenia (Dolan et al., 1999), and it is therefore unlikely that the neuropsychological deficits found in the HR group will correlate greatly with any specific neuro-anatomical sites.

In summary the follow-up analyses confirmed and strengthened the results reported in Chapter 5. Against a background of general impairment, the HR group demonstrated circumscribed deficits in the domains of executive function, and learning and memory, at baseline and follow-up, suggesting these be robust findings.

CHAPTER SEVEN: THE ASSESSMENT OF HAND PREFERENCE IN THE GROUPS

DEFINITION AND METHODOLOGICAL ISSUES.

HANDEDNESS

7.1. Lateralisation

Broca (1861) was the first to attract widespread attention to cerebral dominance, noting that lesions in a group of people with aphasia all lay in specific regions on the left side of the brain. It became clear that the human brain was asymmetrical. The role of the left hemisphere in language seemed to fit in naturally with the predominant use of the right hand by the majority of individuals. It was assumed that verbal and manual dominance were two aspects of the same function, that right handers had left cerebral dominance for language and that left handers had right cerebral dominance for language. However this view was contested by the discovery of the phenomenon known as crossed aphasia, where left Handers sometimes developed aphasia with left hemisphere lesions and that right handers sometimes became aphasic after right hemisphere lesions. It is now known that verbal and manual dominance are not always controlled by the same hemisphere (Zangwill, 1960; Satz, 1980). Thus motor dominance, predominantly discussed in terms of handedness is not exclusively an indicator of cerebral dominance for language as was previously thought.

7.2. Lateral preference measurement

The majority of people are dextral, preferring the right hand for unimanual tasks such as writing, drawing and throwing, there are also sinistrals, preferring the left hand for such tasks and ambidexterals who have no consistent preference for either hand. This has been the conventional view of hand preferences, however there are those (Annett, 1970; Oldfield, 1971) who believe that handedness is not a discrete variable but in distributed along a continuum from strong right handers through various levels of right/mixed/left preferences to strong left handers. Essentially any definition of handedness will depend on the instrument or method used in its assessment. For research purposes handedness has been measured in several different ways (Beaton, 1985) including; self report, where subjects simply state whether they consider themselves right, left or mixed handed; the hand used for writing is taken as the preferred hand; the demonstration method, where the subject performs a number of unimanual tasks and the hand most often used is denoted the preferred hand; questionnaires, where the subjects fill in a

questionnaire concerning hand usage. None of these methods are perfect, and the differing findings may due to the different methods employed.

7.3. Theories of handedness

There are many theories to describe the genesis of handedness. The major concern of most of these theories is how to accurately account for the occurrence of left handedness. As most people are right handed the occurrence of left handedness has been viewed with mystique. The reasons why left handedness occurs at all has been the driving force of many theorists with some believing it to be a pathological state, a possible marker for early cerebral insult, representing incomplete cerebral dominance, genetically determined, a natural state in some cases and representing pathology in others. The theories are numerous and disparate.

7.3.1. Birth stress hypothesis

There are many studies to suggest that left-handedness is a result of birth stress or obstetric complications (e.g. Bakan et al., 1973). Left handedness was associated with birth order, with those first born and 4th or later born being more likely to be left handed than those of other birth orders (Bakan, 1971, 1977; Leviton and Kilty, 1976). It was proposed that these are high-risk birth orders with more risk of maternal pregnancy complications in those first born and an associated increased risk with increased maternal age in those 4th or later born. This finding has failed to be replicated (Hubbard, 1971; Schwartz, 1977; Hicks et al., 1978; Searleman et al., 1989; Dellatolas et al., 1991). Significant associations have been found between non-right handedness and low IQ (Porac et al., 1980; Zangwill, 1960), language delay (Orton, 1937; Bishop, 1983), and learning disabilities (Bishop, 1983; Geschwind and Behan, 1982; Stephens et al., 1967). Ross et al. (1992), using the demonstration method to determine handedness, found a 12% increase in non-right handedness a group of premature children. They found that the handedness of these children differed from their parents which itself conformed to the general population trends. The authors concluded that among premature children events occurring in utero or perinatally, might override hereditary factors in determining hand preference. They did not report a gender effect. Saigal et al. (1992) found that the proportion of non-right handedness

was significantly higher for a group of extremely low birth weight children (<1,000gms) compared to children born at term. The authors did not find any gender effect. O'Callaghan et al. (1987) in a prospective study, was among the first to confirm the relationship between handedness and extreme prematurity. Other authors have reported similar findings (Ross et al., 1987; Marlow et al., 1989). Schwartz (1988) found that decreased Apgar scores were associated with an increase in non-right handedness at age 2 years. Left handedness or non-right handedness has been found to be associated with neurological disorders such as epilepsy (Silva and Satz, 1979), autism (Soper and Satz, 1984) and cognitive deficit (Satz, 1972, 1973; Geschwind and Behan, 1984). Bakan (1991) reported an increases of left handedness in the offspring of mothers who smoked during pregnancy and suggested that oxygen deficiency may be the cause. Annett and Ockwell (1980) found no evidence for a link between birth stress and left handedness, furthermore they state that left handedness is a natural human variant and not a "pathological state". Levy and Gur (1980) found left eye dominance to be correlated with birth stress. Familial sinistrality is assumed to be less frequent among left handers who have sustained birth stress compared to those who have not (Satz et al., 1985). Bakan et al. (1973) found there to be an increase in familial sinistrality among left handers who had sustained birth stress and suggested that proneness to birth stress may be associated with familial factors.

7.3.2. Prenatal and neonatal indicators of left handedness

Churchill et al. (1962) studied 1,102 cases all born within a 20 month period in one obstetric unit, cases were classified according to birth position whether right-occipito-anterior (ROA; turned towards the right) or Left-occipito-anterior (LOA; turned towards the left). At 2 years the children were examined for handedness and it was found that 62% of the left handers were born in the ROA position. Annett and Ockwell (1980) suggested that this finding may represent that congenital asymmetries of the neuro-muscular organization of the foetus influence its position in the antepartum period. Barnes (1975) reported that slowness to establish regular breathing immediately after birth was more frequent in children found at three years to be left-handed or ambidextrous. Barnes suggested this reflected a more sensitive temperament in the potential left handers. Hepper et al. (1990) reported "we have found evidence of a

behavioural asymmetry in the foetus- a preference for sucking the thumb of the right hand". Using ultrasound scanning they found that 5.4% of 224 foetuses had a clear bias for sucking the left thumb. They reported that the intrauterine position of the foetus had no effect on thumb preference, but thumb-sucking preference was associated with neonatal head position. They interpreted their finding as evidence for the presence of behavioural asymmetries before birth, supporting genetic theories more than the birth stress hypothesis. Dryden (1991) in response to Hepper's report, suggested that as the right upper limb generally receives blood through a vessel that arises more proximally from the aorta than the supply to the left upper limb, thus the development of the right upper limb might be sufficiently more advanced over that of the left to promote early preference of the right thumb. He suggested that "all this sounds more like an epigenetic, rather than a genetic explanation of earlier asymmetries" (Dryden, 1991). The inverted writing posture has also been associated with birth stress in males, it was found that left handed males who experienced birth stress were more than twice as likely to write in the inverted position as nonstressed left handed males (Searleman et al., 1982).

7.3.3. Neuropathological theories of left handedness

Shifts from dextrality may result from alterations in the neural connections supporting right handedness, in the normally expected cerebral asymmetries or disruption of the usual maturational process. Abnormalities of cerebral structure have been found in association with non right handedness . Witleson and colleagues reported that individuals with left or mixed handed preferences demonstrated corpus callosal differences in size and shape, compared to right-handers (Witleson, 1985, 1989; Witleston and Nowakowski, 1991; Witleson and Goldstein, 1991). Witleson and Goldstein (1991) suggested that naturally occurring axon loss during early brain development might be a mechanism involved in determining hand preference and associated hemisphere asymmetries. The total area of the corpus callosum was found to be large in mixed and left handers than in right handers (Witleson , 1985). It was suggested that the larger callosal connection underlies the greater bi-hemispheric representation of language function in left handers. This finding was confined to males and was most pronounced in the area of the isthmus. Witleson and Goldstein (1991)

suggested that this finding indicated reduced axon loss in males and that lateralization changes toward right-handedness with increases in axonal loss over time. The theory that an increasing trend toward right handedness is a secondary consequence of normal maturational process has received much support (Corballis and Morgan, 1978; Morgan and Corballis, 1978; Corballis, 1983; Galaburda et al., 1987; Geschwind and Galaburda, 1987). From this follows the theory that if right sidedness occurs as a function of the normal maturation of the nervous system, any delay or disruption in development could result in an increased proportion of left handers. There is evidence that individuals with Klinefelter's syndrome have slower maturational growth rates (Stewart et al., 1979, 1982) and also that the incidence of non-right handedness in this group is increased compared to age matched normal controls (Netley and Rovet, 1984). The left hand is more vulnerable to perinatal damage than the right (Liederman, 1983). Bakan (1978) suggested that hypoxia induced by perinatal stress, results in pyramidal motor dysfunction of the left hemisphere. Sinistrality has been found to be associated with rates of physical maturation in non clinical samples (Coren et al., 1986).

The theory of the existence of a syndrome of pathological left handedness was put forward by Satz (1972). The syndrome is described "a pattern of correlative changes in lateralization in individuals with known or suspected brain damage" Orsini and Satz (1986). The syndrome is characterized by; atypical or right sided hemispheric speech representation; hypoplasia of the right foot; hypoplasia of the right hand; motor impairment of the non-dominant hand; impaired visuospatial functions relative to preserved verbal cognitive function; low probability of familial sinistrality or similar to that of normal dextrals (Satz, 1972). The syndrome is believed to be caused by a lesion that is predominantly left sided with an onset before 6 years of age and which encroaches on the critical speech zones of the fronto-temporo-parietal cortex (Orsini and Satz, 1986). The authors found right sided speech representation in 90% of sinistrals with evidence of early left sided lesions. Thus there appears to be grounds for the theory that left or mixed handedness in some instances is representative of underlying cerebral pathology.

Another theory which links left handedness with maturational factors and neuropathology is that proposed by Geschwind and Galaburda (1987). In this theory the role of chemical intrauterine factors is emphasized rather than direct effects of birth/perinatal stress. The authors suggest that due to the findings of structural asymmetries of the brain "there is probably some influence that slows the growth of parts of the left hemisphere so that.....the corresponding regions on the right develop more rapidly", (pg 11). Testosterone or some factor relevant to it was suggested to be related to both left handedness and to autoimmune and developmental disorders (Geschwind and Galaburda, 1987). High levels of testosterone (or progesterone) during foetal development or heightened sensitivity to these prenatal sex hormones, or both are thought to disrupt normal neuronal development. Geschwind and Galaburda's hypothesis was stated "a delay in development of some cortical regions on the left side ....should favour growth of cortical regions on the opposite side and of unaffected regions on the same side. The larger of the two areas will probably have not only more surviving cells but also more extensive bi-lateral connections.." (pg 12). The authors believe that excessive delays in maturation caused by the male related influence, testosterone, could lead to disrupted cortical architecture and to neural connections forming in abnormal locations. Autoimmune diseases were found to be increased in non-right handers (Smith, 1987; Pennington et al., 1987). Geschwind and Galaburda (1987) put forward a convincing argument to account for left and mixed handedness, they address the issue of sexual dimorphism and related phenomena and do not rule out the importance of genetic factors in the process.

7.3.4. Genetic theories of handedness

There are a number of reasons to believe that handedness is determined by genetic factors, these reasons were outlined in detail by Levy (1976). Firstly, a number of functional and behavioural asymmetries are present at and around the time of birth and therefore handedness cannot be explained by theories of learning. Secondly handedness is related to anatomical asymmetries of the brain, and if these asymmetries are under genetic control it would be surprising if handedness was not also under such control. Thirdly, family studies of handedness suggest a genetic factor (Annett, 1973), familial sinistrality is important in relation to recovery from aphasia (Luria, 1970). Fourthly,

children adopted by left handed parents are not more likely to be sinistrals than those adopted by dexterals (Carter-Saltzman, 1980). Therefore handedness in not learned intra-familially. There are many genetic theories of handedness including; Levy and Nagylaki (1972); Annett (1972, 1975, 1978, 1985a and b); McManus (1984, 1985); McManus and Bryden, (1991). The genetic theories have been review by McManus (1991).

7.3.5. The Annett theory of handedness

The Annett theory has gained much acceptance and will be discussed here. Annett's' model, the Right Shift Theory (Annett, 1972), takes the conjunction between laterality and cerebral dominance for language into account. Annett stated that "all that is required to account for the biological bases of human laterality is one systematic factor plus chance" (Annett, 1991). It was proposed that there is a genetic right shift factor, which is responsible for right handedness and left hemisphere dominance in most individuals. Annett believes that chance is sufficient to account for the laterality of hand and brain of humans who lack the RS factor for left hemisphere speech. People lacking the RS factor are expected to develop a preference for either right or left hand with a probability of 0.5, also many would be expected to show mixed eye and foot preferences. Due to societal pressures more than 50%, closer to 60-70% (Annett, 1991), will develop right hand preferences for writing. A small developmental influence would be sufficient to displace the normal distribution of skill asymmetries along to the right, as if a constant were added to all the chance probabilities, giving the left hemisphere an advantage in comparison with the right, and so makes it likely to serve speech. This would increase the probability of hand, foot and eye control by the left hemisphere (Annett, 1991). The theory was further developed from findings with aphasics. It was noticed that the proportion of people with right hemisphere speech when cases of unilateral lesion were studied in series drawn from the general population without reference to handedness is about 9.3% and the majority of these are not left handers but right handed for writing. Annett, assuming that chance was the only factor at work in right hemisphere speakers suggested that there must be another 9.3% with left hemisphere speech who lack the RS factor therefore about 18-19% of the population lack the RS factor. It was proposed that the influence that normally induces

speech in the left hemisphere could depend on a single gene (rs+), in the absence of this factor (rs-) there is only chance. Some people will have one copy of the gene (rs+ - genotypes), some will have no copy (rs - - genotypes) and some must have two copies (rs+ + genotypes). Normal lateral asymmetries of the hand and brain depend on chance, and in almost 20% of the population, those of (rs - - genotype) chance is the only determinant involved. In some people (rs + - genotype), almost 50% of the population asymmetries depend on chance and a factor, which induces speech development in the left hemisphere by giving a mild handicap to the right hemisphere, and thus slightly weakening the left hand. In slightly more than 30% of the population those of (rs + + genotypes) asymmetries depend on chance and a double dose of the factor handicapping the right hemisphere and weakening the left hand (Annett, 1991). The proportions suggested a genetic balanced polymorphism (Annett, 1999) with heterozygote advantage for the right shift locus. Indeed evidence has been found to support this theory, where strong dexterals were found to have slow left hands rather than fast right hands in a hand skill task (Kilshaw and Annett, 1983). Pathological influences can disrupt this genetically mediated programme of lateralization also the chance factor allows for the occurrence of discordant handedness in monozygotic twins which is estimated to be approximately 21.69% (McManus 1991). A recent paper provided evidence that specific genes on chromosome 6 are related to left-handedness (Gangestad et al., 1996).

Left handedness is not necessarily related to cerebral impairment (Hardyck and Petrinovich, 1977; Crinella et al., 1971; Annett and Ockwell, 1980; Hicks et al., 1979). Life span studies have shown that the population percentage of left handers diminishes steadily, so that they are under-represented in the oldest age group (Coren and Porac, 1979; Fleminger et al., 1977a; Porac et al., 1980b; Smart et al., 1980; Dellatolas et al., 1991). Lansky et al. (1988) reported that 11.3% of 18-39 year olds were left handed versus 4.7% in 40-80 year olds. The reasons for reduced dextrality with age have been discussed in the literature. There have been a number of reports suggesting that left handed subjects disappear from the population due to an increased mortality risk from accidents and susceptibility to immune disorder (e.g. Coren and Halpern, 1991). That people become more right handed with age due to cumulative effects of cultural

pressures throughout the life span was investigated by Ellis et al. (1998) but not supported.

7.4. Critique of methods in lateralisation research

Lateral preferences of both a motor (hand and foot) and sensory nature (eye, ear) are thought to be associated with the organization of the brain. The previous overview of the various theories of handedness particularly left handedness or non-right handedness demonstrates the idea of a link between left-handedness/ non right handedness and some pathological state/ disease or disorder/ related to birth stress, reduced survival fitness, low birth weight etc. There is a literature disputing the validity of the concept of handedness as it is related to disorder. Handedness or any lateral preference is defined by the instrument used for its measurement . It has been shown that hand preferences can change depending on the instrument, the number of items included, the criterion for classification into one or other group, the cut off criteria, if a person is forced to give a response or can choose from a series of graded responses, questionnaire versus demonstration (Peters, 1992). Peters demonstrated that the proportion of right-handers to non right handers varies from 1:100 to 92:8 as a function of questionnaire length, graded or forced response to items and cut off criteria. There is wide agreement that different prevalence figures for left-handedness or nonright-handedness results from different classification methods (Annett, 1985; Bryden, 1977,1982). Peters noted that removal of an item from a questionnaire can change prevalence figures by up to 20%. While the prevalence of right handedness is approximately 90% in the normal population (based on self report or writing hand) this prevalence drops to approximately 65% when a multiple item questionnaire is used (Annett, 1972). Also strict cut-off criteria (e.g. 100%) are likely to lead to increased mixed handedness compared to less stringent criteria. There is also evidence of culture differences in reporting hand preferences, with some cultures being less likely to choose extreme responses and with men making less extreme responses than women (Peters, 1992). Peters questions the validity of associating hand preference with disorder "what is the nature of the association between a particular underlying dimension and handedness when individuals can move in and out of the handedness categories depending on selection criterion". Bishop (1990) criticising what she called reporting of spurious associations

between handedness and disorder suggested that specification of cut-offs after inspection of the data was the most likely important source. Bishop, (1990), suggested that there may be a publication bias with negative results not being published and also the use of small sample sizes leads to a high probability of spurious associations. There is also a tendency for handedness to be used as a "bonus factor" (Fairweather, 1976), where a hand questionnaire is thrown in due to being cheap and easy. If something interesting emerges it is reported if not it is ignored. Sample sizes and cut offs should be set apriori.

Bishop (1983) outlined the various theories relating laterality to developmental disorders. These included a: the view that all left handers are brain damaged, b: the presences of crossed dominance indicates confusion of cerebral dominance, c: cerebral dominance is altered in some manner, d: mixed handedness is an indication of delay in establishing cerebral dominance, having adverse consequences for language development, e: the presence of pathological left handedness. Bishop (1983) talked about two types of mixed handers, those who are mixed due to insufficient practice of the task, and those who are genuinely mixed and mixed in adulthood (inconsistent within task/ test retest preferences). Hand preferences may not be fully established until about 7 years (Coren et al., 1981). In relation to children's preferences, Bishop suggests that in children mixed handedness should be regarded not as a sign of incomplete cerebral lateralization , but as evidence of immature motor and /or cognitive development.

7.5. Handedness in patients with schizophrenia: why is it important

If early development in schizophrenia is disrupted due to genetic/ environmental factors and if patients show a shift in the distribution of laterality this could provide indirect evidence for a neuropathological substrate in some proportion of patients. This neuropathological substrate in some patients may be a result of early brain injury (pathological left handedness), differential rates of brain maturation (Bracha, 1991), and/ or genetic factors. Reduced cerebral lateralisation has been found in those who are left handed or ambidextrous (Foundas et al., 1995) and also in patients with schizophrenia (for review see Petty, 1999) and their relatives (Murray, 1996),

suggesting some genetic influence. Recently a trend towards and excess of mixed handedness has been reported in the relatives of schizophrenic patients (Orr et al., 1999). Crow (1997) describes how schizophrenia may "reflect a breakdown of bi-hemispheric co-ordination of language" and suggests that schizophrenia may be the result of reduced cerebral lateralisation. The Annett right shift theory outlined above has recently been discussed in the context of schizophrenia, Annett (1999) suggested that schizophrenia might be due to a mutated agnosic RS+ gene causing an anomaly of cerebral dominance (suggesting a single gene). Yeo et al. (1999), "hypothesise that the genetic effects on handedness do not result from variation in genes that code for lateralization, as claimed by both Crow and Annett. Rather there exists genetic variation in the precision with which the species-wide developmental design for cerebral asymmetry is expressed." page 203. Yeo et al. suggest that the disrupted lateralization, functional and anatomical, can be understood in light of the theory of developmental instability (DI). Which suggests that some cases of schizophrenia develop due to the genotypes inability to buffer adverse environmental agents and mutations, which cause the individual to veer away from the expected course of development.

Much research has been conducted, investigating the relationship between handedness and schizophrenia, but the results are inconclusive. The literature on lateral preferences in schizophrenia is fraught with contradictions due to the many methodological difficulties outlined above and in Taylor et al. (1982). The focus has mainly been on the assessment of handedness, with eye and foot preferences receiving somewhat less attention. In a recent review of the handedness literature (Satz and Green, 1999) it was reported that the majority of studies showed an association between non-right handedness and schizophrenia, providing some support for the leftward or atypical shift in the distribution of handedness in patients with schizophrenia. Differences between studies regarding subject selection, diagnostic variations, method of eliciting preferences, and classification of handedness may account for these varying results. Case control studies of handedness and its relationship to schizophrenia are outlined in Table 7.1. The number of schizophrenic patients and controls, the diagnostic system employed, the handedness instrument used, and results of the studies are summarised in the table.

Table 7.1. Studies comparing handedness in patients with Schizophrenia and controls

Study	Patients (n)	Controls (n)	Criteria	Handedness assessment	Results
Oddy & Lobstein (1972)	140	497	Not stated	Annett Scale (1970) (Annett)	No Differences
Lishman & McMeekan (1976)	26	3128	ICD	Annett	No Differences
Wahl (1976)	26	18	Not stated	10 manual tasks	No Differences
Dvirskii (1976)	1270	4340	Institute of Psychiatry, USSR	8 items & parent interview	Increased left handedness
Fleminger et al. (1977b)	102	800	ICD-8 (1968)	Annett	Increased right handedness
Gur (1977)	200	200	Mental State examination	23 items	Increased left and mixed handedness
Taylor et al. (1980)	272	800	Present State examination	Annett	Increased right handedness
Nasrallah et al. (1981)	84	82	DSM-III	6 items	Increased left and mixed handedness
Chagule and Masters (1981)	93	150	ICD-8	Annett	Increased non right handedness
Kameyama et al. (1983)	584	688 adults 1041 kids	RDC	Hecaen and De Ajuriaguena (1964)	No differences
Merrin (1984)	52	49	RDC	Crovitz &Jenner	No difference
Shimizu et al. (1985)	1174	4282	DSM III	13 item	No differences
Shan-ming et al. (1985)	225	432	RDC	10 items	Increased non-right handedness.
Foster Green et al. (1989)	93	105	DSM-III	Soper	Increased mixed and ambiguous handedness
Nelson et al. (1993)	72	105	DSM-III	Soper	Increased mixed and ambiguous handedness
Manoach (1994)	71	25	DSM-III	Annett	No differences
Clementz et al. (1994)	58	119	DSM-III	EHI*	Increased left handedness
Cannon et al. (1995)	96	43	DSM-III	EHI	Increased mixed handedness
O'Callaghan et al. (1995)	47	24	DSM-III	EHI	No difference
Taylor and Amir (1995)	163	112	DSM-III	EHI	Increased non-right handedness
Malesu et al. (1996)	120	86	RDC	Annett	No difference
Cannon et al. (1997)	24	3564	DSM III-R	Writing hand	No difference.
Orr et al. (1999)	94	85	DSM III	Annett	Increased mixed handedness

* Edinburgh Handedness Inventory (Oldfield, 1971)

7.6. Correlates of non-right handedness in schizophrenia

Previous studies have attempted to elucidate clinical correlates of left-handedness and /or non right-handedness in schizophrenia. Left handedness has been associated with ventricular enlargement (Andreasen et al., 1982; Katsanis and Iacono, 1989; Clementz et al., 1994), though this finding has been disputed (Randolph et al., 1990). In addition, non-right handedness in schizophrenic patients has been variously associated with clinical correlates. These have included, severity of thought disorder (Manoach et al., 1988; Manoach 1994), paranoid symptomatology (Nasrallah et al., 1981), obstetric complications (Hauser et al, 1985), male sex (Lishman and McMeekan, 1976), tardive dyskinesia (Joseph, 1990), negative family history of sinistrality, and negative family history of schizophrenia (Shimizu et al., 1985), negative symptomatology (see Satz and Green, 1999), earlier age at onset (Dvirskii, 1983). Recent reports have shown an increased incidence of mixed handedness in association with schizophrenia with no increases in strong left-handedness (Green et al., 1989; Nelson et al., 1993). Mixed-handedness has been found to be more common in schizotypal personality disorder (Kim et al., 1992) and "psychosis-prone" individuals (Chapman and Chapman, 1987) than in general population. Although finding no overall differences in handedness between schizophrenic patients and controls, evidence of ambiguous lateralization has been found, such as left /right confusion (Wahl, 1976). Walker and Birch (1970) noted poorly developed preferences for hand and eye usage in schizophrenic children.

Green et al. (1989) using the Annett scale for assessment of handedness, reported an increase in mixed handers/ ambiguous handers among the schizophrenic group. Green et al., found patients to display more within item variability on repeated testing than controls. They reported specifically that 20% more of patients were inconsistent on 3 or more items compared with 3.8% of normal controls. There has been a distinction made between two types of mixed handers; those who are ambidextrous, preferring the right hand for some tasks and the left hand for others; and those who display ambiguous handedness, an inconsistent hand preference for one task on different occasions. Green et al. (1989) suggested that ambiguous handedness in autistic and mentally retarded subgroups might be attributable to severe early bi-lateral brain impairment that prevents

the establishment of manual dominance and cognitive development. Green also reported that males had more ambiguous handedness than females in the patient population but not in the control group. Nelson et al. (1993) reported startling results of the prevalence of mixed handedness in a group of schizophrenic patients falling by 50% on one month re-test, when the tasks involved were demanding, but not when the tasks were less so.

7.7. Eye preferences in schizophrenia compared to controls

There have been conflicting reports regarding eye dominance in the schizophrenia literature. Increased left eye dominance has been reported (Cannon et al., 1997, Gur 1977, Shan-Ming et al., 1985) and also right eye dominance was reported (Kameyama et al., 1983) in schizophrenics who were naturally left handed. Left eye dominance has been associated with later age at onset for the disorder and less time spent in hospital (Gureje, 1988). Crossed hand-eye dominance was found (Oddy and Lobstein, 1972, Shan-Ming et al., 1985) but this finding was also not supported (Lishman and McMeekan, 1976, Gur, 1977). Hand eye concordance was found to be increased in patients with schizophrenia and normal children but not adults (Kameyama et al., 1983). Merrin (1984) assessed eye dominance in patients with schizophrenia and did not report any link between sighting preference and the disorder. Clyma (1972) suggested that occular dominance was not determined by cerebral organisation but by factors such as (but not exclusively) visual acuity however others believe there is a relationship between eye dominance, handedness and cerebral organisation (Porac and Coren, 1981).

7.8. Conclusions

While there are inconsistencies in the literature, the weight of evidence suggests that patients with schizophrenia do differ from the general population, showing different handedness distributions than controls. However, to date there is no meta-analysis of the literature of handedness and schizophrenia, which could give some estimate of the number of negative unpublished studies there might be. The conclusion that this is due to disturbance of lateralization and brain organization remains tentative, in view of the vast differences in methodological procedures.

7.9. The aims of the current study:

1. To measure handedness and to compare the three subject groups in this respect. (Given the reported association between handedness and schizophrenia, albeit often inconsistent, it is important to search for such an association in HR groups, as it may reflect disturbed cerebral organisation and the findings might give a clue to the mechanisms by which schizophrenia develop. The presence of such an association might reflect a vulnerability to schizophrenia in some, or a general inherited characteristic of those at risk for schizophrenia.) Also to examine the differential effects on handedness categorisation of the type of scale used (Annett, 1970; Oldfield 1971), and the definition of handedness employed (i.e. a quantitative laterality quotient, discrete categorisation computed from various cut-off points of the laterality quotient, or a categorical classification).

2. To measure consistency of hand preference on repeated administration of tasks in a single session and to address the question of mixed/ambiguous hand preference.

3. To compare handedness measures derived from demonstration of hand preference to verbal recall of hand preference.

4. To measure consistency of hand preference over time (at baseline and at 18 month follow-up).

5. To examine eye preferences and foot preferences between the groups, and to investigate any relationship between crossed hand/eye dominance and subject group.

6. To examine the relationship between handedness and socio-demographic variables, family history for schizophrenia, and symptoms as rated on the Present State Examination.

7.10. METHOD

7.10.1. Hand Preferences

Hand preferences were measured using a scale that combined both the Edinburgh Handedness Inventory (Oldfield, 1971) and the Annett Handedness Questionnaire (Annett, 1970). This new scale was specifically compiled for this study and comprised 16 items to assess hand preference and a further two items to assess eye and foot preference. Subjects were requested to demonstrate which hand they would use to carry out each of the tasks. Appropriate props were provided for the subjects. The hand used to do the task was recorded. The tasks were repeatedly administered in a quasi-random fashion (three times in total) so that stability and consistency of response could be measured, similar to the Hand Preference Demonstration Test of Green et al. (1989b) and Nelson et al. (1993). In addition each of the subjects were requested to give verbal responses as to which hand they would use to do various tasks. Eye preference was evaluated on two occasions within the session by asking the individual to look through a small hole in a piece of A4 size paper and by rolling up a piece of paper and asking the person to look through it as though it were a telescope. Foot preference was observed when the subject kicked a football across the room and also by verbally responding to the question 'which foot do you kick with?' The combined scale is shown in Appendix 3, 7.1.

The Edinburgh Handedness Inventory, contains 10 items relating directly to handedness and two further items; foot preference when kicking, and eye preference. Participants were asked to demonstrate how they would perform each task. The traditional scoring for the EHI is to score right hand always (++ is entered in the right column), right hand mostly (+ is entered in the right column), left hand always (++ is entered in the left column), left hand mostly (+ is entered in the left column) or both hands equally (+ is entered into both columns). This scoring can be implemented when a verbal response is requested. When the subject is required to demonstrate hand usage either the right or left hand is chosen for the task with mixed

responses being relatively rare. Using the demonstration method forces more lateralised responses.

7.10.1.1. Edinburgh Handedness Inventory

A quantitative and qualitative measure of handedness was derived from the EHI. A laterality quotient (Oldfield, 1971) was calculated for each individual. The laterality quotient (L.Q.) was calculated according to the formula:

$$L.Q. = \frac{E\,x(i,R) - E\,x(i,L)}{E\,x(i,R) + E\,x(i,l)}$$

Where X(i,R) and X(i,L) are the number of +'s for ith item in the Right and Left columns respectively, (Oldfield, 1971).

The L.Q. is a quantitative measure of handedness. The L.Q. ranges from -100 to +100. Participants with a L.Q. of -100 are strong left handers and participants with a L.Q of +100 are strong right handers. From this the qualitative measure of handedness could be derived.

Foot and eye preference

A qualitative measure was derived for foot and eye preference. Participants were classified as right footed or right eyed if they responded right always; as left footed or left eyed, if they responded left always; mixed footed or mixed eyed, if they did not have a consistent preference for either right or left.

7.10.1.2. Annett Handedness Scale (1970)

The Annett (1970) scale included 12 items. In classifying handedness using the Annett method, a qualitative measure of handedness is derived. The subjects classified as "mixed" handers by Annett in her samples always showed a definite preference for the left hand for at least one of the actions when the other responses were always right. This means that if a subject responds that they use the right hand to do most of the tasks but their response to one or more task is 'either hand', the individual is classified as right handed. If they respond mostly as 'left hand' but also respond to one or more as 'either hand' they are classified as left handed. Only when

at least one of the items is carried out by the opposite hand to that carrying out all other tasks is the person categorised as mixed handed.

Identical analyses were carried out for the two scales for comparative purposes and to evaluate the effect of choice of scale and scoring criteria on handedness categorisation. From the repeated demonstration of tasks, the stability of hand preference was calculated and compared across groups. Also the hand preference questionnaire was repeated at second assessment point so the stability of hand preferences across time could be calculated.

7.10.2. Statistical analysis

The data analysis was conducted in SPSS 8.0.0 (SPSS, 1997). Laterality quotients were calculated using the formula outlined in the method section. Non-parametric statistics were used throughout some of the data generated was categorical (qualitative handedness descriptions) and the laterality quotients were not normally distributed. Kruskal-Wallis oneway analysis of variance was conducted when investigating differences across groups on laterality quotients. The Friedmans test, a non-parametric repeated measures analysis of variance was conducted to assess within group changes across demonstration trials at baseline assessment measuring within session consistency. The Wilcoxon signed ranks test was conducted for paired within group assessment of differences between the two scales. 100%, 90%, and 80% cut-off criterion were chosen, to evaluate the effect of different definitions of handedness on hand classification. Participants were classified as right handed if the L.Q. was greater than or equal to + cut-off point eg. +100, and left handed if the L.Q was less than or equal to - 100, and as mixed handed if the L.Q. was less than e.g. +99 and greater than -99.

Chi-square analysis was used to assess differences between the groups on categorical measures of handedness. To assess change between demonstration and verbal recall of items, McNemar tests were conducted. Spearman's rank order correlations were used to correlate the laterality quotients with the socio-demographic, symptom, and family history variables. Principal components factor analysis with varimax rotation with Kaiser normalisation was conducted on the data

in order to investigate the factor structure of both scales. Gender differences were tested but were not evident for any of the analyses and for this reason both genders were analysed together.

7.11. RESULTS

7.11.1. Round one; baseline assessment

Displayed in Tables 7.2, 7.3, and 7.4 are the number and percentage of subjects with each hand preference (right, left, or mixed) for each item from both scales for demonstration one (Table 7.2), demonstration 2 (Table 7.3) and demonstration 3 (Table 7.4). The results of the verbal recall are presented in Table 7.5. Foot and eye preference was measured twice in the session, at first demonstration, and during the verbal recall section. The results are displayed in Tables 7.2 and 7.5. Displayed in Tables 7.2 to 7.5 is the number and percentage of right, left, and mixed handed responses for each of the tasks from both scales for each demonstration trial and for verbal recall. First demonstration trial is presented in Table 7.2. The percentage of controls using the right hand for tasks ranged from 64.3% for opening a jar to 93.3% for throwing, using a scissors, holding a tennis racket, and hammering a nail. The percentage of right handers in the high-risk group ranged from 53.4% for opening a jar to 92.4% for hand used to hold a scissors. In the patient group the % of right handers ranged from 64.7% for threading a needle to 94.1% for holding a spoon, using a scissors, knife, match and hammer. The number and percentage of right, left, and mixed handed responses for the groups on each task for demonstration trials 2 and 3 are presented in Tables 7.3 and 7.4. In Table 7.5. the verbal recall of tasks is presented. Information about 'which hand would you use to take the lid off a jar?' was not systematically collected. For the controls the % of right handers ranged from 65.5% for threading a needle to 93.5% for hammering a nail, and cutting with a scissors. In the high-risk group the range was similar, 66.4% for taking the lid off a box, up to 91.6% for holding a tennis racket. Patients response of right handed ranged from 66.7 for taking a lid off a box to 96.3% for cutting with a scissors, using a knife, and holding tennis racket. Thus there was a wide variety in the percentages of right handers when categorisation was based on any individual items. The findings suggest that some

Table 7.2. Round one assessment of handedness, first demonstration of tasks; number and percentages presented (percentages are presented in bold).

ITEM O=Oldfield A=Annett	CONTROL			HIGH RISK			PATIENT		
	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED
WRITE (O,A)	27 **90**	3 **10**		107 **89.9**	12 **10.1**		15 **88.2**	2 **11.8**	
DRAW (O)	27 **90**	3 **10**		107 **89.9**	12 **10.1**		15 **88.2**	2 **11.8**	
THROW (O, A)	28 **93.3**	2 **6.7**		109 **91.6**	10 **8.4**		15 **88.2**	2 **11.8**	
SCISSORS (O, A)	28 **93.3**	2 **6.7**		110 **92.4**	9 **7.6**		16 **94.1**	1 **5.9**	
TOOTHBRUSH (O, A)	25 **83.3**	3 **10.0**	2 **6.7**	106 **89.1**	11 **9.2**	2 **1.7**	15 **88.2**	1 **5.9**	1 **5.9**
KNIFE (O)	27 **90**	3 **10**		109 **91.6**	10 **8.4**		16 **94.1**	1 **5.9**	
SPOON (O)	26 **86.7**	4 **13.3**		106 **89.1**	13 **10.9**		16 **94.1**	1 **5.9**	
BROOM (O,A)	23 **76.7**	7 **23.3**		96 **80.7**	22 **18.5**	1 **0.8**	12 **70.6**	5 **29.4**	
MATCH (O,A)	27 **90**	3 **10**		104 **87.4**	15 **12.6**		16 **94.1**	1 **5.9**	
BOX (O)	22 **73.3**	7 **23.3**	1 **3.3**	79 **66.4**	38 **31.9**	2 **1.7**	14 **82.4**	2 **11.8**	1 **5.9**
TENNIS (A)	28 **93.3**	2 **6.7**		108 **90.8**	11 **9.2**		14 **82.4**	3 **17.6**	
NEEDLE (A)	20 **66.7**	10 **33.3**		75 **63**	44 **37**		11 **64.7**	6 **35.3**	
SHOVEL (A)	26 **86.7**	4 **13.3**		103 **86.6**	16 **13.4**		14 **82.4**	3 **17.6**	
CARDS (A)	22 **73.3**	8 **26.7**		94 **79**	25 **21**		13 **76.5**	4 **23.5**	
HAMMER (A)	28 **93.3**	2 **6.7**		107 **89.9**	12 **10.1**		16 **94.1**	1 **5.9**	
JAR (A)	18 **64.3**	10 **35.7**		63 **53.4**	55 **46.6**		14 **82.4**	3 **17.6**	
EYE (O)	20 **66.7**	10 **33.3**		75 **63.6**	43 **26.7**		12 **70.6**	5 **29.4**	
FOOT (O)	24 **80**	6 **20**		98 **82.3**	20 **16.8**	1 **0.8**	15 **88.3**	2 **11.8**	

Table 7.3. Round one assessment of handedness, second demonstration of tasks; number and percentages presented (percentages are presented in bold).

ITEM	CONTROL			HIGH RISK			PATIENT		
	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED
WRITE (O,A)	27 **93.1**	2 **6.9**		104 **90.4**	11 **9.6**		15 **88.2**	2 **11.8**	
DRAW (O)	27 **93.1**	2 **6.9**		103 **89.6**	12 **10.4**		15 **88.2**	2 **11.8**	
THROW (O, A)	28 **96.6**	1 **3.4**		105 **91.3**	10 **8.7**		16 **94.1**	1 **5.9**	
SCISSORS (O, A)	28 **96.6**	1 **3.4**		107 **93**	8 **7**		17 **100**		
TOOTHBRUSH (O, A)	26 **89.7**	2 **6.9**	1 **3.4**	103 **89.6**	11 **9.6**	1 **0.9**	15 **88.2**	1 **5.9**	1 5.9
KNIFE (O)	27 **93.1**	2 **6.9**		106 **92.2**	9 **7.8**		16 **94.1**	1 **5.9**	
SPOON (O)	28 **96.6**	1 **3.4**		100 **87**	14 **12.2**	1 **0.9**	16 **94.1**	1 **5.9**	
BROOM (O,A)	26 **89.7**	3 **10.3**		93 **80.9**	22 **13.6**		13 **76.5**	4 **23.5**	
MATCH (O,A)	27 **93.1**	2 **6.9**		100 **87**	15 **13**		16 **94.1**	1 **5.9**	
BOX (O)	22 **75.9**	7 **24.1**		73 **63.5**	42 **36.5**		14 **82.4**	2 **11.8**	
TENNIS (A)	28 **96.6**	1 **3.4**		105 **91.3**	10 **8.7**		16 **94.1**	1 **5.9**	
NEEDLE (A)	21 **72.4**	8 **27.6**		72 **62.6**	43 **37.4**		12 **70.6**	5 **29.4**	
SHOVEL (A)	27 **93.1**	2 **6.9**		98 **85.2**	17 **14.8**		15 **88.2**	2 **11.8**	
CARDS (A)	21 **72.4**	8 **27.6**		89 **77.4**	26 **22.6**		14 **82.4**	3 **17.6**	
HAMMER (A)	28 **96.6**	1 **3.4**		103 **89.6**	12 **10.4**		16 **94.1**	1 **5.9**	
JAR (A)	17 **60.7**	11 **39.3**		68 **59.1**	47 **40.9**		12 **70.6**	5 **29.4**	
EYE (O)	24 **77.4**	7 **22.6**		99 **70.21**	41 **29.1**	1 **0.7**	22 **84.6**	4 **15.4**	

Table 7.4 Round one assessment of handedness, third demonstration of tasks; number and percentages presented (percentages are presented in bold).

ITEM	CONTROL			HIGH RISK			PATIENT		
	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED
WRITE (O,A)	27 **93.1**	2 **6.9**		103 **90.4**	11 **9.6**		15 **88.2**	2 **11.8**	
DRAW (O)	27 **93.1**	2 **6.9**		103 **90.4**	11 **9.6**		15 **88.2**	2 **11.8**	
THROW (O, A)	28 **96.6**	1 **3.4**		104 **91.2**	9 **7.9**	1 **0.9**	15 **88.2**	2 **11.8**	
SCISSORS (O, A)	28 **96.6**	1 **3.4**		106 **93**	8 **7**		17 **100**		
TOOTHBRUSH (O, A)	26 **89.7**	2 **6.9**	1 **3.4**	102 **89.5**	10 **8.8**	1 **0.9**	15 **88.2**	1 **5.9**	1 **5.9**
KNIFE (O)	27 **93.1**	2 **6.9**		104 **91.2**	10 **8.8**		16 **94.1**	1 **5.9**	
SPOON (O)	26 **89.7**	3 **10.3**		100 **87.7**	14 **12.3**		16 **94.1**	1 **5.9**	
BROOM (O,A)	25 **86.2**	4 **11.4**		90 **78.9**	24 **21.1**		13 **76.5**	4 **23.5**	
MATCH (O,A)	27 **93.1**	2 **6.9**		99 **86.8**	15 **13.2**		15 **88.2**	2 **11.8**	
BOX (O)	23 **79.3**	6 **20.7**		73 **64**	41 **36**		12 **70.6**	4 **23.5**	
TENNIS (A)	28 **96.6**	1 **3.4**		104 **91.2**	10 **8.8**		16 **94.1**	1 **5.9**	
NEEDLE (A)	19 **65.5**	10 **34.5**		76 **66.7**	38 **33.3**		11 **64.7**	6 **35.3**	
SHOVEL (A)	27 **93.1**	2 **6.9**		97 **85.1**	17 **14.9**		15 **88.2**	2 **11.8**	
CARDS (A)	20 **69**	9 **31**		88 **77.2**	26 **22.8**		15 **88.2**	2 **11.8**	
HAMMER (A)	28 **96.6**	1 **3.4**		103 **90.4**	11 **9.6**		16 **94.1**	1 **5.9**	
JAR (A)	17 **60.7**	11 **39.3**		63 **55.3**	51 **44.7**		13 **76.5**	4 **23.5**	

Table 7.5. Round one assessment of handedness, verbal recall of tasks; number and percentages presented (percentages are presented in bold).

ITEM	CONTROL			HIGH RISK			PATIENT		
	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED	RIGHT	LEFT	MIXED
WRITE (O,A)	28 **90.3**	3 **9.7**		130 **90.9**	13 **9.1**		25 **92.6**	2 **7.4**	
DRAW (O)	28 **90.3**	3 **9.7**		127 **88.8**	13 **9.1**	3 **2.1**	24 **88.9**	2 **7.4**	1 **3.7**
THROW (O, A)	24 **77.5**	2 **6.4**	5 **16.1**	126 **88.1**	6 **4.2**	11 **7.7**	25 **92.6**	1 **3.7**	1 **3.7**
SCISSORS (O, A)	29 **93.5**	2 **6.5**		133 **93**	10 **7**		26 **96.3**		1 **3.7**
TOOTHBRUSH (O, A)	22 **70.9**	5 **16.1**	4 **12.9**	126 **88.1**	14 **9.8**	3 **2.1**	21 **77.8**	2 **7.4**	4 **14.8**
KNIFE (O)	27 **87.1**	3 **9.7**	1 **3.2**	130 **90.9**	12 **8.4**	1 **0.7**	26 **96.3**	1 **3.7**	
SPOON (O)	25 **80.6**	3 **9.7**	3 **9.7**	114 **80.4**	12 **8.4**	16 **11.2**	25 **92.6**	2 **7.4**	
BROOM (O,A)	23 **74.2**	5 **16.1**	3 **9.7**	110 **76.9**	23 **16.1**	9 **6.3**	18 **66.7**	4 **14.8**	5 **18.5**
MATCH (O,A)	28 **90.3**	3 **9.7**		124 **86.7**	16 **11.2**	3 **2.1**	25 **92.6**	1 **3.7**	1 **3.7**
BOX (O)	22 **71**	5 **16.1**	4 **12.9**	95 **66.4**	30 **21**	18 **12.6**	23 **85**	2 **7.4**	2 **7.4**
TENNIS (A)	28 **90.3**	1 **3.2**	2 **6.5**	131 **91.6**	12 **8.4**		26 **96.3**	1 **3.7**	
NEEDLE (A)	23 **65.8**	7 **20**	1 **2.9**	99 **69.2**	38 **26.6**	6 **4.2**	19 **70.4**	8 **29.6**	
SHOVEL (A)	23 **74.2**	5 **16.1**	3 **9.7**	118 **82.5**	19 **13.3**	6 **4.2**	20 **74.1**	4 **14.8**	3 **11.1**
CARDS (A)	25 **80.6**	6 **19.4**		125 **87.4**	15 **10.5**	3 **2.1**	25 **92.6**	2 **7.4**	
HAMMER (A)	29 **93.5**	2 **6.5**		107 **89.9**	12 **10.1**		16 **94.1**	1 **5.9**	
FOOT (O)	21 **70.0**	3 **10.0**	6 **20.0**	114 **79.7**	14 **9.8**	15 **10.5**	24 **88.9**	3 **11.1**	

scale items are less likely to elicit strong lateral biases than other, probably more difficult tasks (this has been reported often e.g. Nelson et al., 1993 Annett 1985b).

The data were next combined into a more manageable form. Laterality quotients (LQs) were calculated for each subject group for each demonstration session, for verbal recall and for combined demonstration of hand preference, according to the formula outlined in the method section (Oldfield, 1971). LQs were calculated for the 10 item EHI scale and for the 12 items of the Annett scale. For verbal recall on the Annett scale only 11 items were included as verbal recall of hand used to unscrew the lid of a jar was not systematically collected. The LQs for baseline data are displayed in Figures 7.1-7.18. The LQs for the 3 demonstration trials totalled for the Oldfield scale are given in Figs. 7.1-7.3, and for the Annett scale in Figs. 7.4-7.6, for the controls, high-risk, and patient groups respectively. The LQs for demonstration trial 1 for the Annett and Oldfield scales for the groups are displayed in Figs 7.7-7.12. Finally the LQs for the verbal recall are presented for each scale and group in Figs 7.13-7.18. All histograms were set to scale of the high-risk group, for ease of comparability. The means and standard deviations are given beside each figure.

The comparison of laterality quotients across groups at baseline is presented in Table 7.6. The LQs were compared across the groups using the Kruskal-Wallis one way analysis of variance. Data is presented for the comparison of total demonstrations trials for the Annett and Oldfield scales and for each demonstration trial and verbal recall separately for each scale. The mean rank, median, and 25^{th} and 75^{th} percentiles are presented along with the numbers in each group considered in the analysis. There were no significant differences between the groups in terms of the laterality quotients.

A repeated measures non-parametric analysis of variance (Friedman's test) was conducted on the data across demonstration trials to assess whether the laterality quotients changed significantly from one administration of tasks to the next, therefore measuring within session consistency (data not presented in tabular form). There were no significant differences in laterality quotients, generated from the EHI,

across demonstration trials (D1, D2, D3) for the controls (χ^2=4.22, df 2, p=0.12), the high risk group (χ^2=3.94, df 2, p=0.14),

Fig 7.1. LQ for the Oldfield 10 scale total demonstration trials; controls

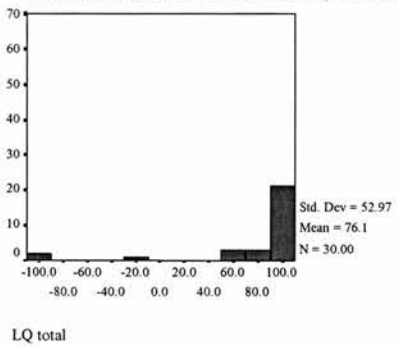


Fig 7.2. LQ for the Oldfield 10 scale total demonstration trials; high risk

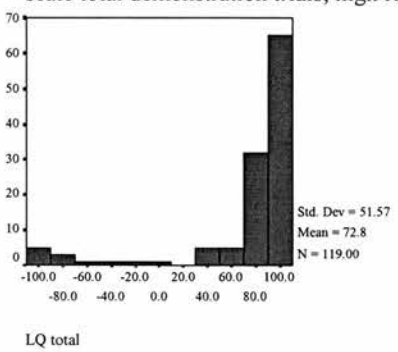


Fig 7.3. LQ for the Oldfield 10 scale total demonstration trials; patients

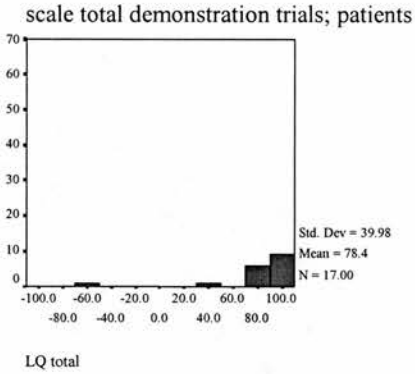


Fig 7.4. LQ for the Annett 12 item total demonstration trials; controls

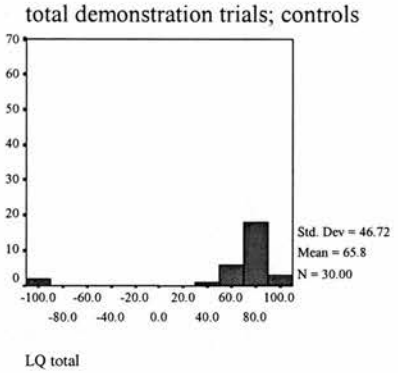


Fig 7.5. LQ for the Annett 12 item total demonstration trials; high risk

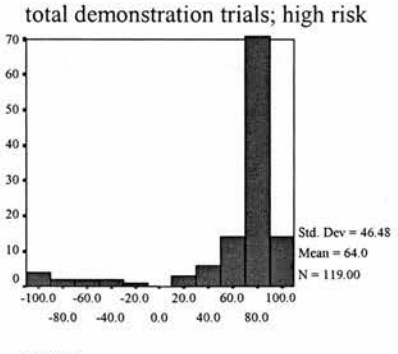


Fig 7.6. LQ for the Annett 12 item total demonstration trials; patients

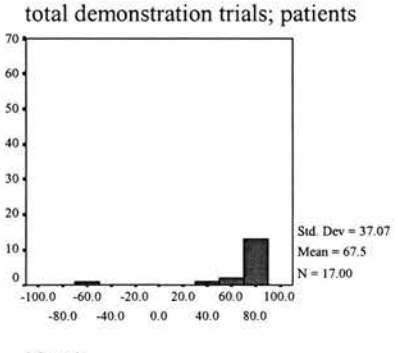


Fig 7.7. LQ for the Oldfield 10 item demonstration trial one; controls

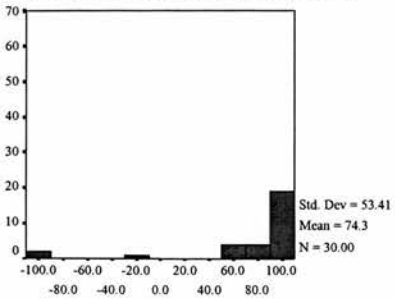


Fig.7. 8. LQ for the Oldfield 10 item demonstration trial one; high risk

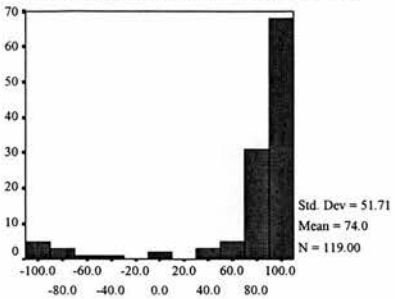


Fig 7.9. LQ for the Oldfield 10 item demonstration trial one; patients

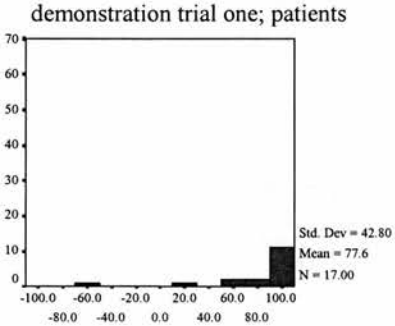


Fig 7.10. LQ for the Annett 12 item demonstration trial one; controls

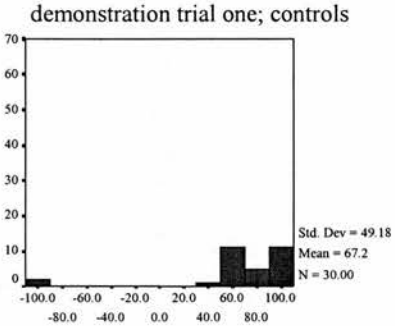


Fig 7.11. LQ for the Annett 12 item demonstration trial one; high risk

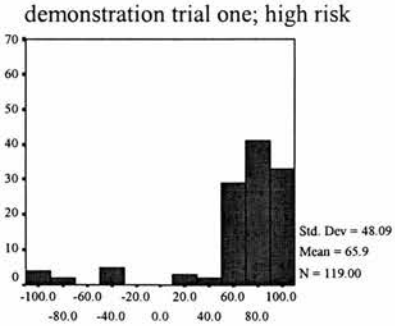


Fig 7.12. LQ for the Annett 12 item demonstration trial one; patient

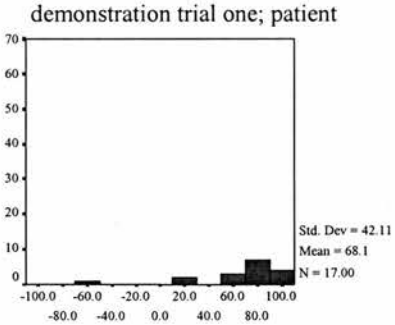


Fig 7.13. LQ for the Oldfield 10 item verbal recall; controls

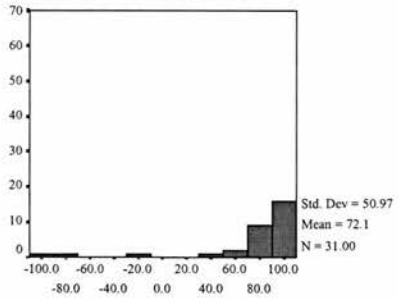


Fig 7.14. LQ for the Oldfield 10 item verbal recall; high risk

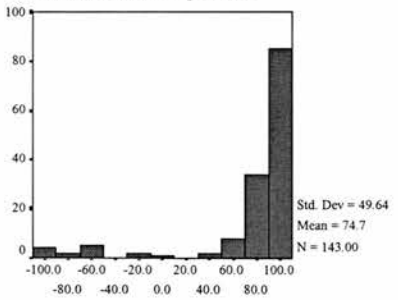


Fig 7.15. LQ for the Oldfield 10 item verbal recall; patient

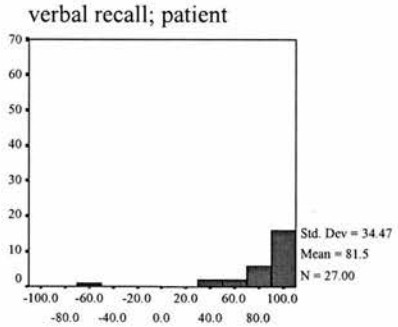


Fig 7.16. LQ for the Annett 12 item verbal recall; controls

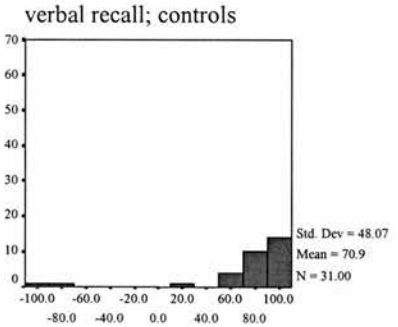


Fig 7.17. LQ for the Annett 12 item verbal recall; high risk

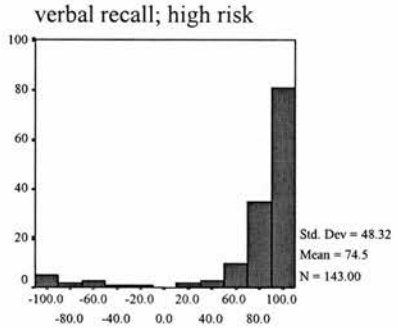
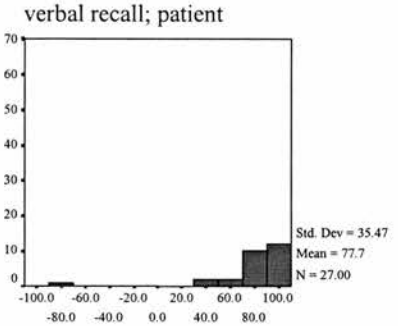


Fig 7.18. LQ for the Annett 12 item verbal recall; patient



Figures 7.1 to 7.18 Laterality quotients displayed by scale and group

In Figures 7.1 to 7.18 the Y axis represents the number of persons and the X axis represents the laterality quotients ranging from –100 to +100.

or the patient group (χ^2=2.82, df 2, p=0.24). Similarly for LQs generated from the Annett scale there were no significant differences across demonstration trials for the controls (χ^2=2.67, df 2, p=0.26), and the high-risk group (χ^2=0.84, df 2, p=0.66).

However, there was a significant difference across trials for the patient group (χ^2=6.33, df 2, p=0.04), where the LQ for demonstration 1 (D1) was significantly lower than that for D2 and D3, suggesting that initially the patient group showed less literalised responses but on subsequent trials, they had more lateralised responses.

A measure of change or within session inconsistency of hand preference on each item was calculated, across the three demonstration sessions (Table 7.7) and between the demonstration and verbal recall sessions (Table 7.8). If items were conducted with the same hand for demonstrations 1, 2 and 3 responses were deemed stable. If any item was conducted with the opposite hand to the other trial/trials it was considered unstable. From Table 7.7 it can be seen that the percentage of individuals whose hand preference changed between demonstration trials for individual items, ranged from 3.4 to 11.3 for controls, from 0.9 to 8.0 for the HR group, and for patients from 5.9 to 23.6. The item 'taking a lid off a box', was the most unstable item for all groups. Overall the responses were stable across items 98% of the time for controls, 97% for HR, and 96% for patients.

From Table 7.8 it can be seen that the percentage of control subjects changing hand preference between demonstration trial one and verbal recall ranged between 3.6% and 32.2% (44.4% for foot preference). In the high-risk group the percentage of subjects changing stated hand preference was 0.9% to 41.4% (44.8% for foot preference). In the patient group this range was 5.9 to 52.9% (23.5% for foot preference). For all groups the largest number of people displaying inconsistent preference between demonstration and verbal recall was for the item 'taking a lid off a box'. This item belongs to the EHI (Oldfield, 1971). Overall, change between demonstration trial one and verbal recall occurred in 17% of the controls, 15% of the HR group, and 21% of patients.

Table 7.6. Laterality quotients: comparisons across groups at time one with Kruskal Wallis tests

Laterality Quotient	Group	Mean Rank	Median	Percentile (25, 75)	N	χ^2	p
Annett demonstration	Control	**82.37**	76.47	67.49, 89.47	30		
	High Risk	**84.77**	78.95	66.67, 80.00	119	0.457	**0.796**
	Patients	**76.59**	76.47	89.47, 100	17		
Oldfield demonstration	Control	**90.73**	100	73.33, 100	30		
	High Risk	**81.79**	93.33	80.00, 100	119	0.935	**0.627**
	Patient	**82.68**	93.33	75.00, 100	17		
Annett verbal recall	Control	**89.35**	81.81	72.73, 100	31		
	High Risk	**105.02**	90.91	80.95, 100	143	0.2.63	**0.269**
	Patient	**93.07**	81.82	78.95, 100	27		
Oldfield verbal recall	Control	**93.4**	90.00	70.00, 100	31		
	High Risk	**101.55**	90.00	78.95, 100	143	0.901	**0.637**
	Patient	**106.80**	100	70.00, 100	27		
Oldfield demonstration 1	Control	**85.12**	100	75, 100	30		
	High Risk	**82.84**	100	80, 100	119	0.097	**0.953**
	Patient	**85.24**	100	70, 100	17		
Oldfield demonstration 2	Control	**91.47**	100	80, 100	29		
	High Risk	**78.27**	100	80, 100	115	2.303	**0.316**
	Patient	**81.62**	100	80, 100	17		
Oldfield demonstration 3	Control	**91.91**	100	80, 100	29		
	High Risk	**78.36**	100	80, 100	114	2.68	**0.262**
	Patient	**75.36**	80	75, 100	17		
Annett demonstration 1	Control	**83.67**	83.33	66.67, 100	30		
	High Risk	**83.43**	83.33	66.67, 100	119	0.001	**1.00**
	Patient	**83.71**	83.33	66.67, 91.67	17		
Annett demonstration 2	Control	**83.22**	83.33	66.67, 100	29		
	High Risk	**79.85**	83.33	66.67, 100	115	0.277	**0.871**
	Patient	**84.97**	83.33	66.67, 100	17		
Annett demonstration 3	Control	**79.74**	83.33	66.67, 100	29		
	High Risk	**80.35**	83.33	66.67, 100	114	0.054	**0.973**
	Patient	**82.79**	83.33	66.67, 100	17		

Table 7.7. Round one % of stable responses across demonstration tasks (3 presentations of items) as a measure of inconsistent hand preference

ITEM	CONTROL % Stable (N)		HIGH RISK		PATIENT	
WRITE	100 (29)		100 (114)		100 (17)	
DRAW	100 (29)		99.1 (113)	0.9 (1)	100 (17)	
THROW	100 (29)		96.5 (110)	3.5 (4)	94.1 (16)	5.9 (1)
SCISSORS	100 (29)		100 (114)		100 (17)	
TOOTHBRUSH	100 (29)		98.2 (112)	1.8 (2)	100 (17)	
KNIFE	100 (29)		99.1 (113)	0.9 (1)	100 (17)	
SPOON	93.1 (27)	6.9 (2)	95.6 (109)	4.4 (5)	100 (17)	
BROOM	96.6 (28)	3.4 (1)	93.9 (107)	6.1 (7)	100 (17)	
MATCH	100 (29)		100 (114)		94.1 (16)	5.9 (1)
BOX	89.7 (26)	11.3(3)	93.0 (106)	7.0 (8)	76.5 (13)	23.6 (4)
TENNIS	100 (29)		100 (114)		100 (17)	
NEEDLE	93.1 (27)	6.9 (2)	93 (106)	7.1 (8)	94.1 (16)	5.9 (1)
SHOVEL	100 (29)		98.2 (112)	1.8 (2)	100 (17)	
CARDS	96.6 (28)	3.4 (1)	96.5 (110)	3.5 (4)	94.1 (16)	5.9 (1)
HAMMER	100 (29)		99.1 (113)	0.9 (1)	100 (17)	
JAR	100 (28)		92.0 (104)	8.0 (9)	94.1 (16)	5.9 (1)

Table 7.8. Round one % change from verbal recall to demonstration of tasks as a measure of inconsistent hand preference

ITEM	CONTROL		HIGH RISK		PATIENT	
WRITE	100 (28)		100 (111)		100 (17)	
DRAW	100 (28)		98.2 (109)	1.8 (2)	100 (17)	
THROW	67.9 (19)	32.1 (9)	80.2 (89)	19.8 (22)	64.7 (11)	35.3 (6)
SCISSORS	100 (28)		97.3 (108)	2.7 (3)	94.1 (16)	5.9 (1)
TOOTHBRUSH	82.1 (23)	17.9 (5)	90.1 (100)	19.9 (11)	58.8 (10)	41.2 (7)
KNIFE	100 (28)		97.3 (108)	2.7 (3)	94.1 (16)	5.9 (1)
SPOON	82.1 (23)	17.9 (5)	82.9 (92)	17.1 (19)	16 (94.1)	5.9 (1)
BROOM	71.4 (20)	28.6 (8)	80.2 (89)	19.8 (22)	58.8 (10)	41.2 (7)
MATCH	96.4 (27)	3.6 (1)	92.8 (103)	7.2 (8)	94.1 (16)	5.9 (1)
BOX	67.9 (19)	32.2 (9)	58.6 (65)	41.4 (46)	47.1 (8)	52.9 (9)
TENNIS	89.3 (25)	10.7 (3)	99.1 (110)	0.9 (1)	88.2 (15)	11.8 (2)
NEEDLE	82.1 (23)	17.9 (5)	79.3 (88)	20.7 (23)	88.2 (15)	11.8 (2)
SHOVEL	78.6 (22)	21.4 (6)	90.1 (100)	9.9 (11)	70.6 (12)	29.4 (4)
CARDS	85.7 (24)	14.3 (4)	85.6 (95)	14.4 (16)	82.4 (14)	17.7 (3)
HAMMER	96.4 (27)	3.6 (1)	98.2 (109)	1.8 (2)	100 (17)	
EYE	89.7 (26)	10.3 (3)	90.3 (102)	9.7 (11)	93.8 (15)	6.3 (1)
FOOT	65.5 (19)	44.5 (10)	65.2 (75)	44.8 (40)	76.5 (13)	23.5 (4)

Laterality quotients for the Annett and the Oldfield scales were compared, within each group, for demonstration trials 1, 2, 3, and verbal recall. The results are presented in Table 7.9. Wilcoxon signed ranks test was conducted for each group separately

Table 7.9. Laterality quotients: Paired assessment of Annett versus Oldfield questionnaire

Laterality Quotient	Group	Mean Rank	Median	25th, 75th P	N	Z	p
Oldfield demonstration 1	Control	**6.20 (+)**	**100**	**75, 100**	30	-2.584	**0.010**
V Annett demonstration 1		**11.36 (-)**	**83.33**	**66.67, 100**			
	High Risk	**23.85 (+)**	**100**	**80, 100**	119	-5.547	**0.000**
		49.53 (-)	**83.33**	**66.67, 100**			
	Patient	**8.17 (+)**	**100**	**70, 100**	17	-1.774	**0.076**
		7.32 (-)	**83.33**	**66.67, 91.67**			
Oldfield demonstration 2	Control	**8.40 (+)**	**100**	**80, 100**	29	-2.581	**0.010**
V Annett demonstration 2		**11.81 (-)**	**83.33**	**66.67, 100**			
	High Risk	**27.84 (+)**	**100**	**80, 100**	115	-4.861	**0.000**
		45.30 (-)	**83.33**	**66.67, 100**			
	Patient	**5.75 (+)**	**100**	**80, 100**	17	-1.578	**0.115**
		7.56 (-)	**83.33**	**66.67, 100**			
Oldfield demonstration 3	Control	**7.67 (+)**	**100**	**80, 100**	29	-3.081	**0.002**
V Annett demonstration 3		**11.00 (-)**	**83.33**	**66.67, 100**			
	High Risk	**24.60 (+)**	**100**	**80, 100**	114	-4.393	**0.000**
		46.34 (-)	**83.33**	**66.67, 100**			
	Patient	**5.10 (+)**	**80**	**75, 100**	17	-1.405	**0.160**
		8.19 (-)	**83.33**	**66.67, 100**			
Oldfield verbal recall	Control	**13.50 (+)**	**90**	**70, 100**	31	-0.678	**0.498**
V Annett verbal recall		**8.73 (-)**	**81.81**	**72.73, 100**			
	High Risk	**52.17 (+)**	**90**	**78.95, 100**	143	-0.203	**0.839**
		41.74 (-)	**90.91**	**80.95, 100**			
	Patient	**10.15 (+)**	**100**	**70, 100**	27	-1.492	**0.136**
		9.67 (-)	**81.82**	**78.95, 100**			

For demonstration trials 1, 2, and 3 there was a significant difference between the scales for the high-risk and control group but not for the patients. In all cases the Oldfield scale yielded higher laterality quotients that the Annett scale as can be seen from the median scores. In terms of verbal recall of items, no differences existed between the scales for any group.

In Table 7.10 data from the Oldfield scale is presented. The numbers of right, left, and mixed handers was compared across the groups by means of chi-square analyses for the three different cut-off criteria. The analysis was limited to demonstration trial 1 (it had the most number of subjects compared to d2 and d3) and the verbal recall condition, to reduce the amount of statistical analyses. The purpose of this analysis

was to evaluate whether changing the classification criteria would cause changes in differences across groups and if it would greatly alter the numbers in each handedness category. For all groups the lowest rate of right handedness was found when using the 100% cut-off criteria in the verbal recall condition (controls 38.7%, high-risk 46.2%, patients 55.6%). The highest rate of right handedness was found for all groups in the demonstration trial with 80% cut-off criteria (controls 76.7%, high-risk 81%, patients 76.5%). Groups did not differ significantly from each other in terms of their handedness distribution for any of the classification criteria.

Table 7.10. Laterality quotients: Oldfield handedness classification compared across groups according to differing cut-off criteria

Laterality Quotient	Control	High Risk	Patient	χ^2	Df	p
Demonstration 1 100% cut-off						
Right	18 (60.0)	66 (55.5)	10 (58.8)			
Left	2 (6.7)	5 (4.2)	0 (0)	1.567	**4**	**0.815**
Mixed	10 (33.3)	48 (40.3)	7 (41.2)			
Demonstration 1 90% cut-off						
Right	19 (63.3)	68 (57.1)	11 (64.7)			
Left	2 (6.7)	5 (4.2)	0 (0)	1.902	**4**	**0.754**
Mixed	9 (30.0)	46 (38.7)	6 (35.3)			
Demonstration 1 80% cut-off						
Right	23 (76.7)	97 (81.5)	13 (76.5)			
Left	2 (6.7)	8 (6.7)	0 (0)	2.938	**4**	**0.568**
Mixed	5 (16.7)	14 (11.8)	4 (23.5)			
Verbal recall 100% cut-off						
Right	12 (38.7)	66 (46.2)	15 (55.6)			
Left	1 (3.2)	4 (2.8)	0 (0)	2.207	**4**	**0.698**
Mixed	18 (58.1)	73 (51.0)	12 (44.4)			
Verbal recall 90% cut-off						
Right	15 (51.6)	85 (59.4)	16 (59.3)			
Left	1 (3.2)	4 (2.8)	0 (0)	1.44	**4**	**0.837**
Mixed	14 (42.2)	54 (37.8)	11 (40.7)			
Verbal recall 80% cut-off						
Right	22 (71.0)	107 (74.8)	19 (70.4)			
Left	2 (6.5)	6 (4.2)	0 (0)	2.423	**4**	**0.658**
Mixed	7 (22.6)	30 (21.0)	8 (29.6)			

The laterality quotients generated for the items from the Annett scale are presented in Table 7.11. For items from the Annett scale the rate of dextrality was generally lower than that for the Oldfield scale (data presented in Table 7.10) and mixed handedness was generally higher. The rate of left handedness was not greatly changed from Table

7.10. Again the groups did not differ for any of the handedness categories. For controls right handedness ranged from a low of 29% for verbal recall with 100% cut-off, to 67.7% for verbal recall with an 80% cut-off. For the high-risk group the lowest rate of dextrality was 27.7% for demonstration with 100% and 90% cut-offs and the highest was 75.5% for verbal recall with an 80% cut-off. For patients the lowest rate of right handedness, 23.5%, was found for demonstration one 100% and 90% cut-off and the highest rate of 70.4 was found for verbal recall with an 80% cut-off.

The McNemar test was conducted to compare handedness classifications for the two scales within groups. The differences between Table 7.10 and Table 7.11 were all significant.

Table 7.11. Laterality quotients: Annett handedness classification compared across groups according to differing cut-off criteria.

Laterality Quotient	Control	High Risk	Patient	χ^2	Df	p
Demonstration 1 100% cut-off						
Right	9 (30.0)	33 (27.7)	4 (23.5)			
Left	2 (6.7)	4 (3.4)	0 (0)	1.849	**4**	**0.764**
Mixed	19 (63.3)	82 (68.9)	13 (16.5)			
Demonstration 1 90% cut-off						
Right	11 (36.7)	33 (27.7)	4 (23.5)			
Left	2 (6.7)	4 (3.4)	0 (0)	3.010	**4**	**0.554**
Mixed	17 (56.7)	82 (68.9)	13 (76.5)			
Demonstration 1 80% cut-off						
Right	16 (53.3)	72 (60.5)	11 (64.7)			
Left	2 (6.7)	6 (5.0)	0 (0)	1.50	**4**	**0.820**
Mixed	12 (40.0)	41 (34.5)	6 (35.3)			
Verbal recall 100% cut-off						
Right	9 (29.0)	65 (45.5)	9 (33.3)			
Left	1 (3.2)	4 (2.8)	0 (0)	4.702	**4**	**0.319**
Mixed	21 (67.7)	74 (51.7)	18 (66.7)			
Verbal recall 90% cut-off						
Right	14 (45.2)	81 (56.6)	12 (44.4)			
Left	1 (3.2)	5 (3.5)	0 (0)	3.812	**4**	**0.432**
Mixed	16 (51.6)	57 (39.9)	15 (55.6)			
Verbal recall 80% cut-off						
Right	21 (67.7)	108 (75.5)	19 (70.4)			
Left	2 (6.5)	6 (4.2)	1 (3.7)	1.173	**4**	**0.882**
Mixed	8 (25.8)	29 (20.3)	7 (25.9)			

7.11.2 Annett classification system

Handedness on both the Annett scale and the Oldfield scale was classified according to the Annett classification system, with subjects classified as right handed, if all items

were responded to as right, as left if all items received consistent left responses, and as mixed when at least one item was carried out with the opposite hand to the majority. 'Either' responses were not sufficient for a mixed categorisation. Categories of handedness compared across the three groups on each scale at each demonstration trial (1-3) and verbal recall are given in Table 7.12.

Table 7.12. Handedness categorisation according to the Annett classification system

	Control	High Risk	Patient	χ^2	Df	p
Annett Scale; demonstration 1						
Right	11 (36.7)	35 (29.4)	5 (29.4)			
Left	2 (6.7)	4 (3.4)	0 (0)	2.307	**4**	**0.680**
Mixed	17 (56.7)	80 (67.2))	12 (70.6)			
Oldfield Scale; demonstration 1						
Right	20 (66.7)	67 (56.3)	11 (64.7)			
Left	2 (6.7)	5 (4.2)	0 (0)	2.760	**4**	**0.598**
Mixed	8 (26.7))	47 (39.5)	6 (35.3))			
Annett Scale; demonstration 2						
Right	9 (31.0))	33 (28.7)	5 (29.4)			
Left	1 (3.4)	4 (3.5)	0 (0)	0.676	**4**	**0.954**
Mixed	19 (65.5)	78 (67.8)	12 (70.6)			
Oldfield Scale; demonstration 2						
Right	22 (75.9)	61 (53)	10 (58.8)			
Left	1 (3.4)	5 (4.3)	0 (0)	5.776	**4**	**0.217**
Mixed	6 (20.7)	49 (42.6)	7 (41.2)			
Annett Scale; demonstration 3						
Right	10 (34.5)	37 (32.5)	4 (23.5)			
Left	1 (3.4)	4 (3.5)	0 (0)	1.439	**4**	**0.837**
Mixed	18 (62.1)	73 (64.0)	13 (76.5)			
Oldfield Scale; demonstration 3						
Right	21 (72.4)	60 (52.6)	9 (52.9))			
Left	1 (3.4)	5 (4.4)	0 (0)	4.702	**4**	**0.319**
Mixed	7 (24.1)	49 (43.0)	8 (47.1))			
Annett Scale; verbal recall						
Right	18 (58.1)	85 (59.4)	15 (55.6)			
Left	2 (6.5)	6 (4.2)	0 (0)	2.06	**4**	**0.725**
Mixed	11 (35.5)	52 (36.4)	12 (44.4)			
Oldfield Scale; verbal recall						
Right	22 (71.0)	103 (72.0)	20 (74.1)			
Left	2 (6.5)	6 (4.2)	0 (0)	1.66	**4**	**0.798**
Mixed	7 (22.6)	34 (23.8)	7 (25.9)			

In Table 7.12 handedness categories are presented according to the Annett classification system. Subjects were classified as right, left, or mixed handed according to the procedure outlined in the method section. The groups did not significantly differ from each other for any condition of either scale. Again

McNemar tests revealed significant differences for all handedness classifications, between the Oldfield and Annett scales, compared within groups. Subjects were consistently more dextral according to the Oldfield scale than the Annett scale.

The total number of items carried out by the opposite hand, was investigated across the groups. Kruskal-Wallis non-parametric one-way analysis of variance was conducted on the data. The results are reported in Table 7.13. There were no significant differences between the groups for any of the classifications.

Table 7.13. Number of items on each scale carried out by the opposite hand compared across groups

	Control	High Risk	Patient	χ^2	df	p
Annett Scale; demonstration 1						
Median (25^{th}, 75^{th} P)	1.0 (0, 2)	1.0 (0, 2)	1 (0, 1.5)			
Mean (sd)	1.1 (1.15)	1.23 (1.26)	1.18 (1.24)	0.154	2	**0.926**
Range (Min, Max)	4 (0, 4)	6 (0, 6)	4 (0, 4)			
Oldfield Scale; demonstration 1						
Median (25^{th}, 75^{th} P)	0 (0, 1)	0 (0, 1)	0 (0, 1)			
Mean (sd)	0.53 (1.11)	0.58 (0, 1)	0.65 (1.11)	0.840	2	**0.657**
Range (Min, Max)	5 (0, 5)	5 (0, 5)	4 (0, 4)			
Annett Scale; demonstration 2						
Median (25^{th}, 75^{th} P)	1.0 (0, 2)	1.0 (0, 2)	1.0 (0, 2)			
Mean (sd)	1.03 (0.91)	1.23 (1.29)	1.06 (0.90)	0.054	2	**0.973**
Range (Min, Max)	3 (0, 3)	6 (0, 6)	3 (0, 3)			
Oldfield Scale; demonstration 2						
Median (25^{th}, 75^{th} P)	0 (0, 0)	0 (0, 1)	0 (0, 1)			
Mean (sd)	0 (0.90)	0.68 (1.07)	0.59 (0.87)	3.869	2	**0.144**
Range (Min, Max)	4 (0, 4)	6 (0, 6)	3 (0, 3)			
Annett Scale; demonstration 3						
Median (25^{th}, 75^{th} P)	1 (0, 2)	1 (0, 2)	1.0 (0.5, 1.5)			
Mean (sd)	1.28 (1.28)	1.21 (1.27)	1.06 (0.83)	0.000	2	**1.000**
Range (Min, Max)	3 (0, 3)	5 (0, 5)	3 (0, 3)			
Oldfield Scale; demonstration 3						
Median (25^{th}, 75^{th} P)	0 (0, 0.5)	0 (0, 1)	0 (0, 1)			
Mean (sd)	0.52 (1.15)	0.65 (0.93)	0.71 (0.92)	2.660	2	**0.269**
Range (Min, Max)	3 (0, 3)	4 (0, 4)	3 (0, 3)			
Annett Scale; verbal recall						
Median (25^{th}, 75^{th} P)	0 (0, 1)	0 (0, 1)	0 (0, 1)			
Mean (sd)	0.52 (0.93)	0.54 (0.88)	0.56 (0.75)	0.491	2	**0.782**
Range (Min, Max)	4 (0, 4)	4 (0, 4)	3 (0, 3)			
Oldfield Scale; verbal recall						
Median (25^{th}, 75^{th} P)	0 (0, 1)	0 (0, 0)	0 (0, 1)			
Mean (sd)	0.45 (1.15)	0.36 (0.82)	0.41 (0.74)	0.203	2	**0.904**
Range (Min, Max)	6 (0, 6)	5 (0, 5)	2 (0, 2)			

For each scale the degree of change in hand categorisation occurring between demonstration trial one and verbal recall was investigated by means of a McNemar

change test and presented in Table 7.14. The percentage of change between the two conditions is presented. For the Annett scale significant changes form demonstration to verbal recall were found in the high-risk group for the 100%, 90%, and 80% cut-offs. The percentage of change between the two conditions was significant for the HR group for the Oldfield scale at the 100% and the 80% cut-off. Significant change did not occur in either the patient or control groups for either scale.

Table 7.14. Differences between demonstration and verbal recall of hand preference in the groups presented for each scale and differing cut-offs.

	Group	% R to M	% L to M	% M to R	% M to L	McNemar P value
Annett D1 100	**High Risk**	21.9	25.0	29.1	1.3	0.007
V	**Control**	22.2	50.0	11.1	0.0	1.00
Annett VR 100	**Patient**	50.0	---	23.1	0.0	1.00
Annett D1 90	**High Risk**	9.4	25.0	40.5	2.5	0.000
V	**Control**	27.3	50.0	31.3	0.0	1.000
Annett VR 90	**Patient**	25	---	38.5	0.0	0.22
Annett D1 80	**High Risk**	10.0	0	48.7	0.0	0.029
V	**Control**	6.3	0	45.5	0.0	0.219
Annett VR 80	**Patient**	9.1	---	50.0	16.7	no statistics
Oldfield D1 100	**High Risk**	39.1	40.0	23.9	2.2	0.024
V	**Control**	44.4	50.0	22.2	0.0	0.065
Oldfield VR 100	**Patient**	10.0	---	28.6	0.0	1.000
Oldfield D1 90	**High Risk**	19.7	40.0	29.5	2.3	1.00
V	**Control**	26.3	50.0	25.0	0.0	0.29
Oldfield VR 90	**Patient**	18.2	---	50.0	0.0	1.00
Oldfield D1 80	**High Risk**	14.0	25.0	14.3	0.0	0.002
V	**Control**	13.0	0.0	25.0	0.0	0.625
Oldfield VR 80	**Patient**	7.7	---	25.0	0.0	1.000

Wilcoxon signed ranks test was used to examine differences within each group between demonstration trial 1 and verbal recall conditions for the quantitative laterality quotients (see Table 7.10 and 7.11 for figures). For the Annett scale there was a significant difference between the demonstration and verbal recall for the high-risk group (-4.13, p=0.00) but not for the controls (-0.92, p=0.26) or for the patient group (-0.91, p=0.36). Dextral responses were more frequent in the verbal recall compared to the demonstration conditions. For the Oldfield scale, there was a trend

towards a difference between the demonstration and verbal recall for the high-risk group (-1.78, p=0.07) but not for the controls (-1.06, p=0.29) or for the patient group (-0.84, p=0.40).

The data were re-coded to represent those who were strongly lateralised, left and right together versus those who were mixed handed. In Table 7.15 the percentage of each group strongly lateralised is outlined for both scales, for the different cut-offs, and for demonstration trial 1 and verbal recall conditions.

Table 7. 15 % of subjects in each group strongly lateralized

Scale and Cut-off	High Risk %	Control %	Patient %	χ^2
Annett D1 100	31.1	36.7	23.5	NS
Annett D1 90	31.1	43.3	23.5	NS
Annett D1 80	65.5	60.0	64.7	NS
Annett VR 100	48.3	32.3	33.3	NS
Annett VR 90	60.1	48.4	44.4	NS
Annett VR 80	79.7	74.2	74.1	NS
Oldfield D1 100	59.7	66.7	58.8	NS
Oldfield D1 90	61.3	70.0	64.7	NS
Oldfield D1 80	88.2	83.3	76.5	NS
Oldfield VR 100	49.0	41.9	55.6	NS
Oldfield VR 90	62.2	54.8	59.3	NS
Oldfield VR 80	79.0	77.0	70.4	NS

Range from 31.1% to 88.2% in the high-risk group, 32.3% to 83.3% in the controls and from 23.3% to 76.5% in the patient group depending on the criteria used. Chi-square tests revealed no significant differences across groups.

The % change between demonstration one at time one and time two is given in Table 7.16. for the high-risk group and the controls (as patients were seen once only). The overall percentage change for the controls was 10% and 9% for the HR group.

Table 7.16. Round one % change from base line to follow-up on demonstration of tasks as a measure of inconsistent hand preference over time

ITEM	CONTROL % same		HIGH RISK % same	
WRITE	100 (15)		100 (56)	
DRAW	100 (15)		100 (56)	
THROW	93.3 (14)	6.7 (1)	92.9 (52)	7.2 (4)
SCISSORS	100 (15)		100 (56)	
TOOTHBRUSH	86.7 (13)	13.3 (2)	92.9 (52)	7.2 (4)
KNIFE	100 (15)		98.2 (55)	1.8 (1)
SPOON	100 (15)		98.2 (55)	1.8 (1)
BROOM	80 (12)	20 (3)	87.5 (49)	12.5 (7)
MATCH	93.3 (14)	6.7 (1)	98.2 (55)	1.8 (1)
BOX	66.7 (10)	33.3 (5)	78.6 (44)	21.4 (12)
TENNIS	93.3 (14)	6.7 (1)	96.4 (54)	3.6 (2)
NEEDLE	86.7 (13)	13.3 (2)	76.8 (43)	23.2 (13)
SHOVEL	92.9 (13)	7.1 (1)	98.1 (51)	1.9 (1)
CARDS	86.7 (13)	13.4 (2)	87.5 (49)	12.5 (7)
HAMMER	100 (15)		94.6 (53)	5.4 (3)
JAR	71.4 (10)	28.6 (4)	72.7 (40)	27.3 (15)

7.11.4.Relationship between handedness and socio-demographic variables

7.11.4.1. Quantitative analysis

A series of non-parametric Spearman rank order correlations were conducted between the laterality quotients (for both the Annett scale and the Oldfield scale, for demonstration trial one and the verbal recall condition) and socio-demographic variables. None of the socio-demographic variables were associated with the laterality quotients for the control group. Some significant correlations did arise in the high-risk and the patient groups and the data is presented in Table 7.17. The patient data is presented in italics and the HR data is presented in bold. Negative correlations indicate that the presence of the socio-demographic variable is associated with increasing non-dextrality. All significant correlations were in this direction. Lower laterality scores (non-dextrality) in the patients was significantly

associated with time off school due to truancy (p=0.01), social work involvement (p=0.01), being in foster care (p=0.01), and unemployment (0.009). These correlations were significant for both the Annett and the Oldfield scales for the demonstration trials. For the Oldfield demonstration one trial, there was a significant relationship between decreasing dextrality and reading and writing problems (p=0.04), for the HR group. For the verbal recall conditions of both scales, decreasing dextrality was associated with reading/writing problems in patients (p=0.03), with unemployment in patients on the Oldfield scale (p=0.01), and with social work involvement for the Oldfield scale in high-risk subjects (p=0.008). No relationship was observed between the laterality quotients and family history of psychosis.

Table 7. 17 Significant correlations between laterality quotients and socio-demographic variables and family history variables (high-risk subjects in bold and patients in Italics)

	Annett D1		Oldfield D1		Annett VR		Oldfield VR	
	Rho	p	Rho	p	Rho	p	Rho	p
Reading and writing difficulties			**-0.19**	**0.04**	*-0.42*	*0.03*	*-0.42*	*0.03*
Off school	*-0.59*	*0.01*	*-0.56*	*0. 02*				
Social work involvement	*-0.59*	*0.01*	*-0.56*	*0. 02*			**-0.22**	**0.008**
Foster care	*-0.59*	*0.01*	*-0.56*	*0. 02*				
Employment	*-0.62*	*0.009*	*-0.54*	*0.02*			*-0.47*	*0.01*

7.11.4.2. Qualitative analysis

Chi-squared analyses were conducted between the categorical handedness variables defined by the Annett classification system for both scales, and the socio-demographic variables. The groups were analysed separately. The results are presented in Table 7.18. Where there was a significant difference between handedness categories, left, right, or mixed, and the presence or absence of a socio-demographic variable it is given in the Table. For controls the chi-square and p values are given in bold italics, for the HR group, only bold, and italics are used for the patients. For the controls there was a significant excess of reading/writing problems amongst left handers for demonstration trial one of both scales (Annett, p=0.05; Oldfield p=0.03). In the high-risk group for the

Annett demonstration trial, there was an excess of truants among mixed handers (p=0.05) compared to right or left handers, there was also an excess of mixed handers having a history of social work involvement (p=0.02). According to the Annett verbal recall condition there was an excess of mixed handers having a history of social work involvement (p=0.04). Finally for the high-risk group there was a significant excess of mixed handers with a history of reading/writing problems as defined by the Oldfield verbal recall condition. In the patients, according to the Annett demonstration trial, there was an excess of mixed handers who were unemployed (p=0.04). For the Oldfield demonstration trial, there was an excess of mixed handed patients with a history of truancy (p=0.04), a history of social work involvement (p=0.04) and a history of being in foster care (p=0.04). For both the Annett and Oldfield verbal recall conditions, there was a significant excess of mixed handers with a childhood history of reading/writing problems (Annett, p=0.05; Oldfield p=0.006).

Table 7. 18. Significant chi-square values for analysis of the Annett handedness classification and socio-demographic variables

Socio-demographic and family history variables*	Annett D1		Oldfield D1		Annett VR		Oldfield VR	
	χ^2	p	χ^2	p	χ^2	p	χ^2	p
Reading and writing difficulties	*7.35*	*0.02*	*6.70*	*0.03*	*3.87*	*0.05*	**8.19** *7.43*	**0.02** *0.006*
Off school	**5.86**	**0.05**	*4.56*	*0.04*				
Social work involvement	**7.17**	**0.03**	*4.16*	*0.04*	**6.63**	**0.04**		
Foster care			*4.16*	*0.04*				
Employment	*4.01*	*0.04*						

*High-risk subjects in bold, patients in Italics, and controls in bold italics.

7.11.5. Symptoms within the high-risk group and hand preferences

Chi-square analyses were run to investigate whether there were any differences in handedness measures between those with psychotic symptoms, at visit one and those without such symptoms. (The symptom groups are described in chapter 2 in Table 2.6.13.1. In this analysis, no psychotic symptoms were defined as either PSE 0 or 1 and psychotic symptoms were defined as PSE 2,3,or 4). Both the Annett classification system and the Oldfield system, with varying cut-offs, were investigated for

demonstration trial one and verbal recall. No significant differences were found between the symptom groups for categorical handedness measures. Mann Whitney U tests were run to investigate any differences between the symptom groups and the quantitative laterality quotients for symptoms at first visit and again no statistically significant differences were found. Symptoms and handedness were not related in the control group.

7.11.6. The relationship between psychotic symptoms and eye and foot preferences within the high-risk group

The relationship between the presence of psychotic symptoms and eye preference, defined as the eye used to look through a piece of paper rolled up into a tube, was examined. For those without symptoms at first visit, 55.4% were right eyed compared to 80% of those with symptoms at first visit (chi-square=5.65, p=0.02). There was no relationship between foot preference and symptoms. There was no relationship between foot and eye preference and family history variables within the high-risk group.

7.11.7. Incongruous hand/eye dominance

We examined the relationship between subject group and crossed dominance, or incongruous hand/eye dominance. Hand was defined as the writing hand as in other studies (e.g. Cannon et al., 1997). There was no significant difference between the groups for this variable. The rate of incongruous hand/eye dominance was 23.3% in the control group, 29.7% in the high-risk group, and 41.2% in the patient group.

However within the high-risk group, only 16.7% of subjects with PSE symptoms at first visit had congruous hand/eye dominance versus 36.1% of those without symptoms (not significant).

7.12. Discussion

The aim of this chapter was primarily to assess whether group differences existed in terms of lateral preferences, specifically to investigate whether indicies of lateral

preferences are associated with schizophrenia, and with vulnerability to schizophrenia in those at high risk, compared to the normal control group. The approach taken was to investigate the effect of changing the parameters (the definition of lateral preferences) on any association between lateral preference and subject group, in order to assess whether any such relationships are robust findings or are spurious and unreliable methodological artifacts. In order to achieve this, an evaluation of two different scales (Annett, 1970, and Oldfield, 1971) was conducted, using two different methods of eliciting responses (verbal recall and demonstration), which are often used to classify handedness in research populations.

As a lot of data were presented, a summary of the main findings will be detailed in order of appearance in the text. Firstly the rate of hand preference for each item for all trials was outlined (Tables 7.2 to 7.5) and from the Tables it can be seen that some items are less likely to elicit strong lateral responses than others. Secondly no gender differences were found. Lateralisation effects would appear to be a function of task demand, supported by Nelson et al. (1993).

Laterality quotients were computed for verbal recall and demonstration trials for both scales and no group differences were noted (Table 7.6).

Repeated analysis of the 3 demonstration trials showed no evidence of across trial differences in laterality quotients for the any of the groups for the Oldfield scale. For the Annett scale the patients showed significantly greater inconsistency of responses. They had significantly lower laterality quotients, suggesting less dextrality, for the demonstration trial 1 condition compared to trials 2 and 3. This means that the patient group showed less lateralisation on trial one but on subsequent trials, the laterality quotients increased and they appeared more lateralised. This may be due to more inconsistency in hand preference or a delay in establishing reliable responses in the patients. It could also reflect an increase in stereotypical responding, or perseverative motor responding over time, whereby the patients tend to respond to all items with the predominant right handed response (there were no lefthanders in the group).

Stability of responses for individual items was measured across demonstration trials and between demonstration and verbal recall trials. The results showed that responses in all groups were relatively stable over the demonstration trials. The rate of stability for the controls was 98% compared to 97% in the HR group and 96% in the patients. Comparing the demonstration to verbal recall conditions, a greater change was noted in all groups (Table 7.8) suggesting that the two methods are very different in terms of the responses elicited, the percentage of change was 17% for controls, 15% for the high-risk group, and 21% for the patients. This was primarily accounted for by a tendency to respond as right handed in the verbal recall condition compared to the demonstration trials, particularly for items from the Annett scale (medians presented in Table 7.7). This may be a function of familiarity with the item.

Differences between the laterality quotients were examined for each scale and assessed within each group. In summary differences between the scales were seen for the control group and the high-risk group but not for the patients, for demonstration trials, and for verbal recall no differences were found for any of the groups (Table 7.9). Greater degrees of dextrality were found using the Oldfield scale.

When the laterality quotients for both the Annett and Oldfield scales were categorised according to the cut offs of 80%, 90%, 100%, no group differences in the numbers of right, left, or mixed handers were evident for demonstration trial 1 or for verbal recall (Tables 7.10 and 7.11).

Using the Annett classification system no group differences were noted on either scales for demonstration or verbal recall in terms of the rates of right, left or mixed handedness (Table 7.12).

There was no difference between the groups in terms of the number of items carried out by the opposite hand to the predominantly preferred hand (Table 7.13).

Applying cut-offs to the laterality quotients and comparing within groups, the high-risk group showed significant change in handedness categorisation when comparing demonstration trial one and verbal recall for both scales and at different cut-offs. They tended to be more dextral in the verbal recall condition compared to the demonstration trials.

No differences between the groups were found in terms of the rates of strongly lateralised subjects (Table 7.15). However there was a vast difference across the scales and cut-offs and the highest number of lateralised subjects was found for the demonstration trial of the Oldfield scale.

An analysis was conducted to assess for change in responding over time (between the first and second assessment). Demonstration trial one at time one and time two were compared. The rate of change from baseline for all items was 10% for the controls and 9% for the HR group (calculated as the total number of items where preference changed over time, divided by the total number of items for which responses remained stable, multiplied by 100). As follow-up was confined to the HR and Control groups we cannot comment on the rate of change in hand preferences across time in the Patient group, however a previous study suggested that such changes may occur (Nelson, et al., 1993).

There are implications from the analysis for research on handedness. Firstly the type of scale used and method of scoring is important as different estimates of handedness result from varying these characteristics. The manner in which the responses are elicited would appear to have a great impact on the classification of handedness. Verbal call of preferences tends to elicit more dextral responses than the demonstration trials, however the demonstration of items may be more reliable. Moving from demonstration to verbal recall the HR group demonstrated significant changes of handedness category (Table 7.14).

Overall, there was little evidence of group differences no matter which categorisation of handedness was used. However, the patient's responses to the demonstration trials became more consistent over time, which may suggest that in such populations more than one trial might be necessary for responses to stabilise and become more reliable. Alternatively it could be that their responses are more inconsistent initially, and that over time some form of motor perseveration develops were the responses generally become stereotypical and the predominantly preferred hand is used for many tasks in an experimental setting.

The implications are greatest for correlational studies and studies relating handedness to some other factors, particularly within single clinical groups. For example handedness may be correlated with many variables such as age at onset, prognosis, types of symptoms, cerebral structural dimensions or indices of cerebral structural asymmetry. In this study it was shown that estimates of strong lateral hand preferences (the opposite being mixed handedness) ranged from 32% to 83% in the normal control group depending on the scale and criteria used in the definition of lateralisation, so that the very different and inconsistent results would be expected when the estimate of 'lateralisation' is related to other variables.

Differences between the groups did not appear using two different scales and different scoring criteria in the three groups reported here, and this was also found in 10 of the 23 studies comparing patients with schizophrenia to controls and reported in Table 7.1. It is conceivable that some problems that were not so great in our samples may well be exaggerated in other samples. Of key relevance is the difference between the methods of eliciting responses, whether using verbal recall or demonstration of items. In this study the demonstration of items was conducted prior to the verbal recall of preference. This confounds the possibility of discovering the degree to which the recent experience of conducting the tasks has cued the verbal responses. Here we tried to get subjects to conduct tasks using props without telling them that their hand preference was of key interest in order to try to prevent stereotypical responses, for this reason verbal recall of items was requested later. It would be very interesting to study verbal recall and demonstration of tasks in chronic

patients with verbal recall of items as the first task followed by two or three demonstration trials. In these patients it would presumably have been many years since at least some of the items were conducted and it could be predicted that there may be greater differences between verbal recall and demonstration of the items in such groups. Out subjects were young and in the early stages of illness. Nelson et al., (1993) suggested that a subset of patients may be more vulnerable to state mechanisms such as internal stimuli or task demand and that this may lead to changes over time in responses.

We conducted a correlation study between hand preference and socio-demographic variables. For both the Oldfield and the Annett scales, demonstration trial one, decreased dextrality in the patients was associated with time off school due to truancy, more social work involvement in childhood, being in foster care, and being unemployed. For the verbal recall condition of the Oldfield scale, reduced dextrality was associated with reading and writing problems in the patient group. The correlations were quite high, ranging from 0.54 to 0.62 in the patient group. In the HR group reading and writing difficulties were associated with decreased dextrality for the Oldfield demonstration trial, and with social work involvement on the verbal recall, the correlations were lower than in the patient group.

The findings are interesting in light of the many studies, including the British Cohort studies, which have identified premorbid behavioural problems (Done et al., 1994) and language difficulties (Jones et al., 1994) to be more characteristic of pre-schizophrenic individuals compared to controls. These findings have been implicated to support a neurodevelopmental theory of schizophrenia. In addition it has been suggested that mixed handedness, or reduced dextrality, may indicate a delay in establishing cerebral dominance, which may have adverse consequences for language development (Bishop, 1983). It is interesting that these correlations exist most strongly for the patient group.

As noted earlier the patient groups responses were less lateralised in the demonstration trial one condition than on subsequent trials. It is difficult to say whether this represents a phenomenon whereby patients need more practice to establish reliable responses or whether over time some perseveration of motor responses occurs to the preferred hand. Given the experimental/ laboratory based setting of this study, it was not possible to test this, it would need to be examined in real world, ecological setting.

For the qualitative analysis, using the Annett classification system, an excess of reading and writing problems was found among left handed controls. For the high-risk group there was a significant increase in truancy, social work involvement and reading and writing problems, among mixed handers. In the patient group unemployment, truancy, social work involvement, being in foster care, and reading and writing problems were associated variously with mixed handedness. The relationship between family history for schizophrenia and handedness is outlined in chapter 9.

No relationship was found between handedness and symptoms in the HR and control groups. The HR subjects with psychotic symptoms present at first visit, were significantly more right eye dominant (80%) than those with out (55%) such symptoms. This supports the work of Kameyama et al., (1983) who found increased right eye dominance in patients with schizophrenia but is in contrast to others (Cannon et al., 1997; Gur, 1977; Shan-Ming et al., 1985). There was no relationship between footedness and symptoms. Crossed hand/eye dominance has been reported in patients with schizophrenia (Oddy and Lobstein, 1972; Shan-Ming et al., 1985) however in our sample the rate of crossed dominance was not significantly different across the groups, but the controls showed the lowest rate (23%), followed by the HR group (30%) and the patient group (41%). However in the high-risk group crossed dominance was inversely associated with the presence of symptoms.

The findings of associations between indices of decreased lateralisation and childhood behavioural and language difficulties in the patient group supports the theory of a link between disrupted cerebral development and later schizophrenia.

It is proposed that a standard method of defining handedness should be developed for use in research and used consistently by researchers. From the results of this study, it seems quite clear that differences between the groups did not appear with changing definitions of handedness but that changes in the definition greatly altered the rates of hand preference in all groups and this has implications for comparing across study populations, and when correlating preferences with disorders or pathology.

It would appear that the best method of eliciting stable lateral preference responses is to ask the subject to demonstrate the action rather than for them to verbally recall their preference. It is not clear if any one of the scales currently available in the literature is better than any other, although Marian Annett (Annett, 1986) has conducted a lot of research into her scale and the scoring system that should be employed (the revised scoring systems was not utilized in this study as the aim was to try to evaluate hand preferences in the current samples, in a method similar to previous literature). It would appear to be essential to establish an accepted definition of lateral preferences if results are to be comparable across studies. As outlined in Table 7.1, the findings in the literature are inconsistent and this is most likely due to the great diversity in handedness definition and methods of eliciting responses.

The terms lateral preferences and handedness, as currently reported in the literature, describe a range of differing constructs. A consensus agreement on the definition of handedness and lateral preferences to be employed in future studies of schizophrenia (and other areas) could be achieved through peer discussion, and would be a relevant topic for debate at a meeting of schizophrenia researchers.

CHAPTER EIGHT: NEUROPSYCHOLOGICAL ASSESSMENT RESULTS AND PSE SYMPTOMS

RESULTS FROM BASELINE AND FOLLOW-UP ASSESSMENTS

8.1. Organisation of Chapter eight

It must be stressed that the results that appear in this chapter are preliminary and are subject to change as more subjects (as predicted) develop psychotic symptoms or indeed schizophrenia. It will therefore not be possible to make any definite statements about the relationship between symptoms and the neuropsychological assessment results at this time in, or indeed until the subjects have passed through the total period of risk. However, it was felt appropriate to describe the results at this stage, particularly given the importance of the distinction between possible state/ trait markers for schizophrenia. The profiles of neuropsychological performance of subjects with and without PSE rated psychotic symptoms could help illuminate factors that may be solely related to the presence of symptoms or are general characteristics of the HR group. The study PSE classification was outlined in Chapter two, section 2.6.13.

None of the subjects had a defined schizophrenic disorder at the baseline or follow-up assessments. Some subjects had psychotic symptoms, obtaining a study PSE score of 2 or 3, although all saw themselves as well. If the presence of such symptoms indicates the beginning of the development of schizophrenia or psychosis generally, then subjects with symptoms might be the sole source of the neuropsychological differences between the HR and Control groups. In order to investigate this the adjusted composite scores were analysed across all groups controlling for symptoms and outlined in 8.2.5.

By the end of the 5 years of the study, 10 subjects had received a PSE 4 rating, indicating a clinical diagnosis of schizophrenia. A variable was created, called 'symptoms ever', and the 10 are included in this variable. It was felt that at this stage they should not be analysed separately as the numbers will increase in the future, if the genetic predictions hold. The logic being that having a psychotic symptom, some threshold has been crossed and whether this represents a vulnerability state in some, pre- florid psychosis in others, or indeed is in some cases part of normal variation (4 controls had a study PSE rating of 2 or 3, but the presence of such symptoms in the normal population may need a different interpretation) is unclear. These questions cannot be answered by this study at this time point, but they need to be raised. To study the possibility that psychotic symptoms occur as a normal variation in the population, a

full scale epidemiological investigation with long term follow up of a very large random sample of the general population would be required.

Alternatively all those with study PSE psychotic symptoms and those who will develop such symptoms in the future may be the ones at greatest risk for developing schizophrenia and may be the most deviant responders on neuropsychological assessments (however we can not comment on those who will develop symptoms, and become ill in the future).

This chapter is organised into four sections. In section one (8.2) the presence of symptoms is evaluated in terms of the baseline data in univariate and multivariate analyses. In the second section (8.3) the effect of the presence of symptoms on change over time is evaluated using the follow-up data. In the third section (8.4) the effect of symptom change between rounds 1 and 2 is evaluated. In the fourth section (8.5) the breakdown of the socio-demographic variables by symptoms ever rated, is presented.

8.2. Baseline neuropsychological assessment data analysed by symptoms.

8.2.1 Univariate analysis

The presence of psychotic symptoms was evaluated for each individual by means of the Present State Examination (PSE). Subjects were evaluated at baseline assessment and also at each follow-up or when they developed schizophrenia. Firstly, an analysis was conducted to see if those with psychotic symptoms at baseline were different on any baseline neuropsychological measures from those without such symptoms. Those with psychotic symptoms at baseline assessment did not have full blown schizophrenia but had a mixture of psychotic symptoms (the PSE categorisations is outlined in chapter 2, section 2.6.13). Secondly an analysis was conducted to investigate differences within the high-risk group on neuropsychological measures at baseline assessment between those who ever had psychotic symptoms and those who never had such symptoms. Ever having symptoms was defined over the 5 year course of the study including those who went on to obtain a score of 4 on the PSE and were hospitalised for a

schizophrenic disorder. If there were significant differences within the HR group between those with symptoms and those without, then perhaps those who were symptomatic accounted for the differences between the HR group and controls at baseline and at follow-up.

All analyses were conducted controlling for NART where appropriate as the presence of psychotic symptoms are known to affect current functioning and there may be deterioration from pre-morbid levels. In Table 8.1 the analysis for PSE negative (n=113) and PSE positive (n=39) at first assessment are presented. A univariate ANOVA approach was taken with group and gender as factors in the analysis and NART as a covariate, where appropriate. Group by sex and group by NART interactions were tested in the models. No significant group differences were found for any of the IQ variables.

A significant group effect was observed for FAS, however it was not in the expected direction, the PSE negative group produced significantly fewer words on this test than the PSE positive group. There was a significant group by NART interaction also. A significant group effect for vocabulary was noted, even after controlling for NART, however there was also a NART by group interaction. A significant symptom by sex interaction was noted for type A errors on the Hayling Sentence Completion Test (HSCT) and the predicted values from the model plotted by gender and symptom type (present or absent) are presented in Fig 8.1, males in the PSE (2/3) group had higher predicted rank scores than females, the reverse was true for the PSE (0/1) group. Finally there was a significant group effect for RBMT story immediate recall and a trend for delayed recall. In both cases the PSE (0/1) group had higher mean recall scores than the PSE (2/3) group.

Table 8.1. Neuropsychological variables compared across symptom groups (as measured at first assessment) and adjusted for NART (where appropriate).

	PSE (0,1), n=113 Adjusted mean (se)	PSE (2,3), n=39 Adjusted mean (se)	GROUP F	P	SEX F	P	NART F	P
IQ Variables								
Block Design	10.85 (0.24)	11.25 (0.42)	1.24	0.27	7.14	0.01	33.53	0.000
NART	98.71 (0.96)	96.90 (1.66)	0.90	0.34	0.36	0.55		
Verbal IQ	97.44 (1.08)	94.10 (1.87)	2.38	0.12	3.44	0.07		
Performance IQ	100.48 (1.36)	98.98 (2.34)	0.31	0.58	2.80	0.10		
Full Scale IQ	98.61 (1.20)	95.63 (2.07)	1.54	0.22	3.84	0.05		
Spot the Word	9.55 (0.18)	9.32 (0.32)	3.21	0.08	1.26	0.26	89.15	0.000
Executive function								
STROOP 3	23.73 (0.52)	23.41 (0.91)	0.93	0.34	0.09	0.76	20.82	0.000
STROOP 1-3	13.74 (0.52)	13.33 (0.90)	0.08	0.78	0.15	0.70	12.77	0.000
FAS*	37.72 (1.02)	39.42 (1.82)	4.96	0.03	1.98	0.16	28.10	0.000
Animals	15.61 (.41)	15.37 (0.74)	0.01	0.92	13.6	0.00	12.67	0.001
Ln Hayling timeA	16.84 (15.45, 18.40)	21.50 (18.24, 25.62)	0.14	0.71	0.23	0.63	7.39	0.007
Ln Hayling timeB	31.90 (28.22, 36.21)	35.19 (28.22, 44.36)	0.31	0.58	0.00	0.99	2.0	0.16
HSCT type A errors	#3 (0, 0)	3 (0, 0)	0.02	0.90	1.42	0.23	0.006	0.94
HSCT type B errors	#2 (1,1)	2 (1, 1)	0.17	0.68	0.27	0.60	0.22	0.64
HSCT total errors	#4 (1,1)	4.5 (1, 1)	0.05	0.82	0.97	0.33	0.25	0.62
Perceptual motor speed								
Digit Symbol	10.21 (0.23)	9.06 (0.41)	0.07	0.79	4.71	0.03	19.19	0.000
Mental control /encoding								
Digits Forwards	8.43 (0.17)	7.98 (0.30)	1.00	0.32	0.42	0.52	49.87	0.000
Digits Backwards	7.28 (0.21)	7.18 (0.36)	0.27	0.61	1.26	0.26	29.46	0.000
Arithmetic	9.43 (0.20)	8.91 (0.35)	0.26	0.61	1.78	0.18	45.65	0.000
Verbal ability and language								
Vocabulary*	8.49 (0.15)	8.08 (0.26)	5.86	0.02	1.34	0.25	94.00	0.000
Token test	#163 (161, 161)	162.5 (161, 161)	0.37	0.54	0.49	0.48	8.59	0.004
Speed of comprehen.	11.08 (0.26)	10.58 (0.47)	0.57	0.45	0.01	0.91	63.32	0.000
SCOLP	-1.54 (0.29)	-1.24 (0.52)	3.08	0.08	0.58	0.45	1.91	0.17

	PSE (0,1), n=113 Adjusted mean (se)	PSE (2,3), n=39 Adjusted mean (se)	GROUP F	P	SEX F	P	NART F	P
Learning and memory								
RAVLT trial I	6.42 (0.18)	5.89 (0.31)	0.76	0.38	2.29	0.13	1.08	0.30
RAVLT total I-V	50.91 (0.77)	50.01 (1.33)	0.01	0.90	8.42	0.004	16.58	0.000
RAVLT Recall B	6.06 (0.17	5.74 (0.30)	0.09	0.76	0.60	0.44	7.72	0.006
RAVLT Delayed recall	#10 (8, 9)	10.5 (9, 9)	0.16	0.69	6.25	0.01	10.27	0.002
Visual Reproduction Immediate recall	35.59 (34.93, 36.21)	36.58 (35.46, 37.60)	0.13	0.72	0.02	0.89	19.88	0.000
Visual reproduction Delayed recall	33.70 (32.88, 34.46)	34.69 (33.31, 35.92)	0.60	0.44	0.42	0.52	25.21	0.000
RBMT story immediate recall	9.29 (0.29)	7.87 (0.50)	5.21	0.02	5.17	0.02	19.33	0.000
RBMT story delayed recall	8.06 (0.28)	7.01 (0.49)	3.33	0.07	3.01	0.08	21.31	0.000
RBMT standardised score	#22 (20, 21)	21 (19, 19)	1.30	0.25	0.27	0.60	13.63	0.000

*Significant group by NART interactions were noted for FAS and Vocabulary, in both instances, PSE (0/1) had a steeper linear increase in scores with an increase in NART, compared to the PSE + group.

#Median (25^{th}, 75^{th} percentile)

The same analysis was conducted for those ever having symptoms (n=47) versus those never having symptoms (n=108) and the results are presented in Table 8.2. The result of an independent samples t-test showed a trend towards greater NART, WAIS-R Full Scale IQ discrepancies in those who ever had psychotic symptoms. Again there was a significant effect for FAS, however this time the direction of the effect was reversed and it was accompanied by a similar NART by group interaction. There was a trend towards lower vocabulary scores in the PSE (2,3,4) group. Subjects in the PSE (2,3,4) group had significantly lower mean scores on the RBMT story immediate and story delayed recall. There was, in addition, a trend for those with symptoms to have lower mean rank RBMT standardised scores than those without symptoms.

8.2.2. Symptoms by Factor Scores; baseline data

A multivariate analysis of variance was conducted with group (symptoms at first assessment) and gender as factors and NART as a co-variate except in the analysis of Factor 1, which included NART. Significant group differences were found on factor 2 and factor 3. The results are presented in Table 8.3. There was a significant overall main effect for group (psychosis positive or psychosis negative at first assessment), for gender and NART, there were no significant interactions. Those within the psychosis positive group had significantly higher factor scores for factor 2 than the psychosis negative group. The psychosis negative group had significantly higher scores on factor 3 compared to the psychosis positive group. An identical analysis was run for those ever having symptoms compared to those never having symptoms. The results are presented in Table 8.4. Significant group differences were found for factor 3 only. The psychosis negative group had significantly higher factor 3 scores than the psychosis positive group suggesting a verbal memory problem in this group. For the overall model there was a significant group effect, sex effect and NART effect, there were no significant interaction terms.

8.2.3. Composite standardised Z scores; baseline data

Multivariate analysis of variance was conducted with sex and symptom group as factors with NART as a co-variate.

8.2.3.1 Symptoms at first visit

The first analysis involved those with symptoms at first visit versus those without; the results are given in Table 8.5. The overall model was significant with a significant main effect for gender but not for symptom group. There was a significant effect of the covariate NART. Looking at the univariate analysis significant differences between the groups emerged for the analysis involving perceptual motor speed. For perceptual motor speed, the psychosis positive group had significantly lower scores than the psychosis negative group.

8.2.3.2 Symptoms ever

An identical analysis was conducted on the groups, psychotic symptoms never versus psychotic symptoms ever. The results are presented in Table 8.6. While the overall model was significant there was no overall significant multivariate effect for group, but there was for NART and gender. Univariate analyses revealed significantly lower z-scores for the psychotic symptom positive group for perceptual motor speed. Also there was a trend towards poorer memory function in the psychotic symptom positive group compared to the symptom negative group.

8.2.4.Continuous performance test and symptoms

There were no differences on any of the CPT-IP baseline measures between those with and without symptoms, either at first assessment or at anytime. For this reason the baseline data are not presented in Table format.

8.2.5 Effect of the presence of symptoms on the baseline analyses

A concern in this sample is that the presence of symptoms at baseline could be the sole cause of the neuropsychological differences between the groups and that HR status per se, was not. This has major implications for the interpretations of the findings. Are the deficits seen in the HR group purely a result of the presence of symptoms, although the individuals presented as well and did not report any personal difficulties with these symptoms at baseline assessment? In order to investigate this possibility, two multivariate analysis of variance tests were conducted on the NART adjusted composite scores, similar to the analyses presented in Chapter 5, Tables 5.10 and Table 5.11, with the addition of the covariate, presence of symptoms at baseline assessment in the first

MANOVA, and presence of symptoms ever in the second. The patient group were all scored as PSE 4 in the analyses, and the results are presented in the text only.

The analysis investigating the effect of the presence of symptoms at baseline assessment will be described first. There was an overall significant multivariate effect of symptoms (F=3.46, df=5, 192 p=0.005), of group (HR, Control or Patient; F=2.61, df=10, 382, p=0.005), and of gender (F=3.98, df=5, 192 p=0.002). The group by gender interaction was not significant. The test of between subjects effect revealed that the presence of symptoms had a significant effect on the composite, mental control/encoding (F=7.65, df=1, 196, p=0.006) and perceptual motor speed (F=12.93, df=1, 196, p=0.00). There was a significant effect of gender for the mental control/encoding composite only (F=12.79, df=1, 196, p=0.00) There was a significant effect of group for the learning and memory composite only (F=5.56, df=2, 196, p=0.000) Post hoc examination of main effects using the Least Squared Difference method revealed that on the learning and memory composite, all groups differed significantly from each other. The controls had significantly higher mean scores (mean =-0.03, se=0.12) than the HR group (mean=-0.40, se=0.06) who in turn had significantly higher scores than the patient group (mean=-0.81, se=0.20). This confirmed the original findings and suggests that the presence of symptoms is not responsible for the deficits in learning and memory in the HR group relative to the controls.

The second analyses investigated the effect of symptoms ever, on the NART adjusted composite scores. There was an overall significant multivariate effect of symptoms (F=2.32, df=5, 195, p=0.04), of group (HR, Control, or Patient; F=2.22, df=10, 388, p=0.02), and of gender (F=4.15, df=5, 195, p=0.001). The group by gender interaction was not significant. The test of between subject's effects revealed that the presence of symptoms had a significant effect on the composite, mental control/encoding (F=6.87, df=1, 199, p=0.009) perceptual motor speed (F=6.52, df=1, 199, p=0.01), and learning and memory (F=4.05, df=1, 199, p=0.05) and a trend for the language composite (F=3.04, df=1, 199, p=0.08) There was a significant effect of gender for the mental control/encoding composite only (F=12.98, df=1, 199, p=0.00) There was a significant effect of group for the learning and memory composite only (F=4.55, df=2, 199

p=0.01). Post hoc examination of main effects using the Least Squared Difference method revealed that on the learning and memory composite the control group mean was significantly higher than the HR and patient groups but the HR and patient group did not significantly differed from each other. The controls had significantly higher mean scores (mean =-0.06, se=0.12) than the HR group (mean=-0.40, se=0.06) and the patient group (mean=-0.72, se=0.18). Suggesting that as more HR subjects developed symptoms, the relationship between learning and memory and symptoms became more obvious, however symptoms did not explain the group differences. So it appears that learning and memory difficulties are not the solely caused by the presence of symptoms, but they are significantly reduced in the presence of symptoms.

Figure 8.1 Sex by symptom interaction for Hayling type A

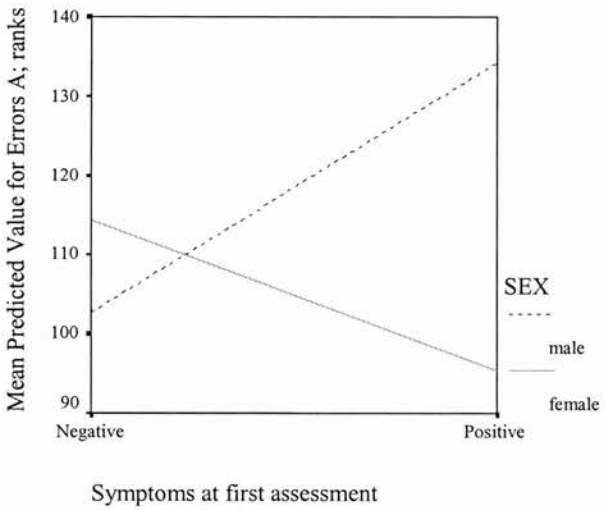


Figure 8.1. Sex by symptom interaction for Hayling type A errors

Table 8.2. Neuropsychological variables compared across symptom groups (symptoms ever rated) and adjusted for NART (where appropriate).

	PSE (0,1), n=108 Adjusted mean (standard error)	PSE (2,3,4), n=47 Adjusted mean (standard error)	GROUP		SEX		NART	
			F	P	F	P	F	P
IQ variables								
Block Design	10.87 (0.24)	11.04 (0.38)	1.44	0.23	6.78	0.01	37.95	0.000
NART	98.64 (9.38)	97.53 (11.30)	0.29	0.59	0.51	0.48		
Full Scale IQ	99.04 (12.98)	95.06 (12.55)	2.14	0.14	3.95	0.05		
Verbal IQ	97.71 (11.51)	94.17 (11.63)	2.06	0.15	4.33	0.04		
Performance IQ	100.88 (14.34)	97.67 (14.47)	1.02	0.31	2.69	0.10		
Spot the Word	9.72 (0.24)	9.09 (0.39)	1.89	0.17	0.33	0.57		
Executive function								
STROOP 3	23.63 (0.526)	23.52 (0.85)	1.16	0.28	0.07	0.79	21.41	0.000
STROOP 1-3	13.66 (0.52)	13.50 (0.84)	0.19	0.66	0.09	0.76	13.45	0.000
FAS*	38.37 (1.03)	38.27 (1.64)	3.91	**0.05**	3.30	0.07	33.64	0.000
Animals	15.78 (0.42)	15.13 (0.67)	0.72	0.79	13.23	0.00	13.82	0.000
Ln Hayling timeA	16.88 (15.45, 18.51)	33.97 (27.66, 42.24)	0.01	0.94	0.14	0.71	9.12	0.003
Ln Hayling timeB	31.68 (27.66, 35.57)	20.17 (15.15, 20.17)	0.14	0.71	0.29	0.59	2.75	0.10
HSCT errors A	#3 (0, 0)	3 (0, 0)	0.75	0.39	1.20	0.27	0.23	0.63
HSCT errors B	#2 (1, 1)	2 (0.75, 1)	0.22	0.64	0.12	0.72	0.59	0.44
HSCT total errors	#4 (1, 1)	4 (1, 1)	0.06	0.81	0.65	0.42	0.86	0.35
Perceptual motor speed								
Digit symbol	10.16 (0.24)	9.27 (0.38)	0.92	0.76	3.81	0.05	21.40	0.000
Mental control /encoding								
Digits Forwards	8.47 (0.18)	8.01 (0.27)	0.27	0.61	0.79	0.37	58.04	0.000
Digits Backwards	7.29 (0.21)	7.12 (0.32)	0.44	0.51	1.34	0.25	30.45	0.000
Arithmetic	9.44 (0.21)	8.98 (0.32)	0.08	0.77	2.09	0.15	50.94	0.000
Verbal ability and language								
Vocabulary	8.55 (0.16)	8.19 (0.24)	3.31	**0.07**	2.65	0.16	105.63	0.000
Token Test	#163 (161, 161)	162 (161, 161)	1.08	0.30	0.70	0.40	9.35	0.003
Speed of Compreh.	11.16 (0.20)	10.63 (0.41)	1.35	0.25	0.49	0.49	75.04	0.00
SCOLP	-1.50 (0.29)	-1.51 (0.49)	2.47	0.12	0.89	0.35	1.79	0.18

	PSE (0,1), n=108 Adjusted mean (standard error)	PSE (2,3,4), n=47 Adjusted mean (standard error)	GROUP F	P	SEX F P		NART F	P
Learning and Memory								
RAVLT trial I	6.47 (0.18)	5.96 (0.28)	0.23	0.63	1.97	0.16	1.97	0.16
RAVLT total I-V	51.43 (0.79)	49.49 (1.22)	0.07	0.78	7.39	0.01	18.65	0.000
RAVLT recall B	6.13 (0.18)	5.64 (0.27)	0.33	0.56	0.69	0.41	9.73	0.002
RAVLT Delayed recall	#11 (9, 9)	10 (8, 8.7)	0.97	0.33	7.83	0.006	9.97	0.002
Visual Reproductions Immediate recall	35.56 (34.89, 36.19)	36.26 (35.20, 37.23)	0.15	0.70	0.003	0.95	22.78	0.000
Visual Reproductions Delayed recall	33.70 (32.88, 34.47)	34.36 (33.05, 35.54)	0.12	0.73	0.24	0.62	28.63	0.000
RBMT story Immediate recall	9.40 (0.29)	7.97 (0.45)	7.01	**0.009**	3.65	0.06	22.29	0.000
RBMT story Delayed recall	8.22 (0.29)	6.92 (0.44)	6.06	**0.01**	1.96	0.16	24.04	0.000
RBMT standardised score	#22 (20, 24)	21 (19, 23.5)	3.18	**0.08**	0.88	0.35	14.98	0.000

*For FAS there was a group by NART interaction and again PSE (0/1) had a steeper linear increase in scores with an increase in NART, compared to the PSE + group.

#Median (25^{th}, 75^{th} percentile)

Table 8.3. Overall differences across the groups for factors 2 to 6 with NART as a co-variate, symptoms at first assessment

	Symptom negative first assessment	Symptom positive first assessment	Sex		Group		Group * Sex		NART	
			F	P	F	P	F	P	F	P
FACTOR 1	0.07 (0.07)	-0.04 (0.13)	0.01	0.92	0.35	0.25	0.39	0.53		
FACTOR 2	-0.17 (0.08)	0.20 (0.15)	7.23	0.01	4.67	0.03	0.54	0.46	14.18	0.00
FACTOR 3	0.07 (0.09)	-0.40 (0.16)	6.77	0.01	6.42	0.01	0.28	0.60	7.92	0.006
FACTOR 4	0.02 (0.10)	0.07 (0.17)	0.35	0.85	6.05	0.83	1.82	0.18	0.37	0.54
FACTOR 5	0.09 (0.09)	0.05 (0.15)	0.31	0.58	0.06	0.80	0.26	0.61	17.99	0.00
FACTOR 6	0.03 (0.09)	-0.13 (0.15)	12.63	0.001	0.81	0.37	1.16	0.28	0.29	0.86

Hotellings T, group effect F=2.27, df 6, p=0.05, sex F=6.05, df 6, p=00, NART F=9.28, df 6, p=0.000, symptoms by sex F=0.83, df 6, p=0.53

Table 8.4. Overall differences across the groups for factors 2 to 6 with NART as a co-variate, symptoms ever

	Symptom negative	Symptom positive ever	Sex		Group		NART		Group * Sex	
			F	P	F	P	F	P	F	P
FACTOR 1	0.07 (0.08)	-0.03 (0.12)	0.09	0.76	0.77	0.38			0.14	0.71
FACTOR 2	-0.17 (0.09)	0.08 (0.13)	5.74	0.02	2.39	0.12	13.79	0.00	0.09	0.77
FACTOR 3	0.10 (0.96)	-0.33 (0.15)	6.88	0.01	5.8	0.02	9.26	0.01	1.53	0.22
FACTOR 4	0.01 (0.10)	0.08 (0.16)	0.003	0.95	0.13	0.71	0.32	0.57	0.93	0.34
FACTOR 5	0.10 (0.09)	0.06 (0.14)	0.18	0.67	0.08	0.78	17.55	0.00	0.98	0.32
FACTOR 6	0.07 (0.09)	-0.17 (0.14)	13.39	0.00	2.03	0.16	0.02	0.88	1.18	0.28

Hotellings T, group effect F=2.08, df 6, p=0.07, sex F=5.71, df 6, p=0.000, NART F=9.66, df 6, p=0.000, symptoms by sex F=0.93, df 6, p=0.47

Table 8.5. Adjusted composite scores analysed according to symptom group; symptoms at first assessment

	PSE negative N=108 Mean (S.E.)	PSE positive N=37 Mean (S.E.)	SEX		Symptom Group		SEX * Symptom Group	
			F	P	F	P	F	P
Executive function	-0.53(0.05)	-0.24 (0.09)	0.64	0.42	0.82	0.37	0.37	0.54
Mental control/ encoding	0.23 (0.06)	0.10 (0.11)	1.98	0.16	1.05	0.31	1.36	0.25
Perceptual motor speed	-0.21 (0.09)	-0.65 (0.15)	6.99	0.01	6.23	0.01	2.39	0.12
Language	-0.12 (0.08)	-0.03 (0.13)	0.19	0.67	0.96	0.33	0.051	0.91
Learning and memory	-0.35 (0.07)	-0.48 (0.12)	0.00	0.96	1.02	0.31	0.17	0.68

Hotellings T; Sex F=3.06, df 5, 0.01; Symptoms, F=1.28, df 5, p=0.28; Sex by symptoms F=0.60, df 5, p=0.70.

Table 8.6. Adjusted composite scores analysed according to symptom group; symptoms ever

	PSE negative N=103 Mean (S.E.)	PSE positive N=45 Mean (S.E.)	SEX		Symptom Group		SEX * Symptom group	
			F	P	F	P	F	P
Executive function	-0.13 (0.06)	-0.27 (0.09)	1.05	0.31	1.91	0.17	0.00	0.98
Mental control/ encoding	-0.24 (0.07)	-0.10 (0.10)	2.65	0.11	1.41	0.24	2.24	0.14
Perceptual motor speed	-0.23 (0.09)	-0.58 (0.14)	5.69	0.02	4.38	0.04	0.60	0.44
Language	-0.17 (0.08)	-0.05 (0.12)	0.51	0.47	2.29	0.13	0.30	0.58
Learning and memory	-0.31 (0.07)	-0.54 (0.10)	0.00	0.96	3.23	0.07	0.06	0.80

Hotellings T; Sex F=2.98, df 5, 0.01; Symptoms ever, F=1.26, df 5, p=0.28; Sex by symptoms ever F=0.02, df 5, p=0.63.

8.3. Neuropsychological change and psychotic symptomatology

The results of the repeated assessments (round one to round two) were analysed by symptoms. The results are given in Table 8.7. Those of the high-risk group who completed a second round of assessments, were divided into two groups based on PSE symptoms. Those who never had a psychotic symptom at either round one or round two and were described as study PSE 0/1, and those who had experienced psychotic symptoms at either round one or two, and described as study PSE 2+. Differences between the groups in terms of current and premorbid IQ as measured at baseline, were assessed by means of t-tests. The psychosis negative group achieved significantly higher scores for VIQ, PIQ, and FSIQ than the PSE positive group. There was no significant group difference on the NART. An interesting finding was a significant difference between the groups in terms of NART, WAIS-R Full Scale IQ discrepancy scores. The mean difference between the groups in terms of NART minus WAIS-R FSIQ was negative for the psychosis negative group, indicating no evidence for a decline from premorbid to current functioning. However for those who had a psychotic symptom (PSE 2+), this difference was positive, indicating pre-morbid IQ to have been higher than the current IQ suggesting that there had been a decline in IQ at sometime for these subjects.

All other analyses were conducted with NART as a co-variate. The ANOVA models included the assessment of main effects for time (round 1 or round 2 assessment), NART, and Group. Also assessment (TIME) by NART and assessment by group interactions were controlled in the model. For the verbal fluency measure names of 4 legged animals, there was a trend for the PSE+ group to recall fewer animal names than the PSE- group. For the delayed recall section of the WMS-R visual reproductions test, there was a significant time by NART interaction, but no main effect for group was evident. For story immediate recall, there was a significant main effect of group with the PSE negative group scoring higher than the PSE+ group on this task, for both assessments. A trend towards this same pattern existed for the story delayed recall, and for the standardised scores of the RBMT. Indicating poorer memory performance in the PSE positive group.

Change from round one to round two on the CPT-IP was analysed by symptoms and assessments (round one and round two). The analyses involving fast numbers and shapes, distracted and non-distracted conditions are presented in Table 8.8. All CPT-IP measures are presented with adjustment for NART. The PSE negative and PSE positive groups were compared. Significant interactions are presented in the last column of Table 8.8.

The two groups exhibited differences in sustained attention. Firstly there was a significant group difference in d' indicating that the study PSE 0/1 group had greater attentional capacity than the study PSE 2+ group. Also, there was a significant group by distraction interaction for d' and ln beta suggesting that the study PSE 0/1 group exhibited greater attentional capacity and respond more cautiously in comparison to the other group under distraction. There was a significant group by stimulus by assessment interaction for both d' and ln randoms where the study PSE 0/1 group improved more between the 2 assessments with the numbers stimuli in comparison to the other group for both variables. The PSE study 2+ group improved for d' and ln randoms with the shape stimuli.

For the CPT-IP fast versus slow conditions, the results are presented in Table 8.9. There were no significant main effects for any of the indices, for log randoms there was a stimulus by speed by round by group interaction. The PSE negative group's ln random score dropped for fast numbers between the first and second round of assessment, but this was not so for the PSE positive group, for slow numbers, there was a greater reduction for the PSE+ group. For fast shapes the PSE positive group showed greater reductions over time compared to the PSE negative group. Both groups showed reduction for slow shapes. For d' there was a stimulus by round by group interaction. Also a speed by group effect was found for log beta, with the PSE+ group showing greater reductions in caution for the slow numbers condition than the PSE negative group.

Table 8.7. Neuropsychological variables compared across groups, repeated analysis (round one to round 2)

	PSE (0, 1) n=60 Mean (sd/se)	PSE (2+) n=20 Mean (sd/se)	EFFECT OF TIME F	P	NART F	P	GROUP F	P
Current IQ								
Verbal IQ	100.68 (12.83)	92.70 (8.63)					3.14	0.003
Performance IQ	103.87 (14.81)	95.55 (12.56)					2.25	0.03
Full Scale IQ	102.37 (14.14)	92.95 (9.13)					3.44	0.007
Block Design 1	11.39 (0.37)	10.89 (0.62)						
Block Design 2	12.51 (0.38)	12.16 (0.64)	0.01	0.92	21.57	0.00	0.36	0.55
Premorbid IQ								
NART	100.26 (10.36)	98.15 (9.53)					0.80	0.43
NART-FSIQ	-2.35 (9.69)	5.20 (9.10)					-3.04	0.003
Spot the Word 1	9.94 (0.27)	9.17 (0.45)						
Spot the Word 2	10.73 (0.26)	10.17 (0.43)	0.00	1.00	81.57	0.00	2.48	0.12
Executive function								
STROOP 3 (R1)	22.92 (0.61)	22.11 (1.04)						
STROOP 3 (R2)	21.61 (0.53)	20.85 (0.90)	3.34	0.07	29.45	0.00	0.58	0.45
STROOP 1-3 1	12.88 (0.80)	12.09 (1.01)						
STROOP 1-3 2	11.71 (0.50)	11.39 (0.84)	3.56	0.06	19.14	0.00	0.33	0.57
FAS (R1)	39.36 (1.57)	38.17 (2.75)						
FAS (R2)	40.96 (1.69)	37.17 (2.96)	0.08	0.78	31.60	0.00	0.62	0.43
Animals (R1)	16.25 (0.68)	13.73 (1.14)						
Animals (R2)	15.94 (0.64)	14.12 (1.06)	0.55	0.46	12.96	0.001	3.56	**0.06**
Ln HSCT time A 1	1.04 (0.02)	1.06 (0.04)						
Ln HSCT time A 2	0.97 (0.02)	1.02 (0.03)	0.62	0.43	9.64	0.003	1.09	0.30
Ln HSCT time B 1	1.25 (0.03)	1.22 (0.05)						
Ln HSCT time B 2	1.17 (0.03)	1.12 (0.05)	0.80	0.37	2.69	0.10	0.61	0.44
Ln HSCT B-A 1	22.56 (3.93)	20.85 (6.69)						
Ln HSCT B-A 2	16.67 (2.76)	13.57 (4.70)	0.001	0.98	0.03	0.86	0.17	0.68
HSCT total errors 1	9.56 (1.49)	8.82 (2.56)						
HSCT total errors 2	4.23 (0.77)	3.33 (1.32)	0.18	0.67	0.02	0.89	0.15	0.70
HSCT errors A 1	4.23 (0.70)	3.63 (1.21)						
HSCT errors A 2	1.88 (0.36)	1.42 (0.62)	0.59	0.44	0.50	0.48	0.34	0.56
HSCT errors B 1	5.33 (1.03)	5.19 (1.77)						
HSCT errors B 2	2.72 (0.60)	2.04 (1.04)	0.13	0.72	0.09	0.76	0.09	0.76

	PSE (0,1) n=60 Mean (sd/se)	PSE (2+) n=20 Mean (sd/se)	EFFECT OF TIME F	P	NART F	P	GROUP F	P
Perceptual motor speed								
Digit Symbol 1	9.99 (0.60)	10.91 (0.36)						
Digit Symbol 2	10.94 (0.57)	11.26 (0.34)	0.06	0.81	14.20	0.00	0.96	0.33
Trails A*	29.27 (1.20)	28.01 (2.06)			7.36	0.008	0.28	0.60
Trails B	57.79 (2.58)	61.35 (4.43)			21.92	0.00	0.48	0.49
Trails B-A	28.52 (2.38)	33.34 (4.09)			13.78	0.00	1.04	0.31
Mental control /encoding								
Digits Forwards 1	8.92 (0.27)	8.69 (0.46)						
Digits Forwards 2	8.69 (0.32)	9.13 (0.55)	1.69	0.20	18.28	0.00	0.04	0.85
Digits Backwards 1	7.29 (0.31)	6.81 (0.520						
Digits Backwards 2	7.74 (0.30)	6.57 (0.51)	0.37	0.54	14.79	0.00	2.49	0.12
Verbal ability and language								
Token Test 1	162.03 (0.22)	161.92 (0.37)						
Token Test 2	162.38 (0.16)	162.24 (0.29)	1.80	0.18	10.29	0.002	0.14	0.71
Speed of Comp. 1	11.60 (0.34)	11.01 (0.56)						
Speed of Comp. 2	12.58 (0.35)	12.54 (0.59)	0.003	0.95	66.60	0.00	0.28	0.60
SCOLP (R1)	-1.53 (0.41)	-1.79 (0.67)						
SCOLP (R2)	-1.72 (0.43)	-1.68 (0.70)	0.01	0.92			0.03	0.87
Learning and memory								
RAVLT trial 1 (R1)	6.77 (0.26)	6.46 (0.44)						
RAVLT trial 1 (R2)	5.75 (0.23)	5.97 (0.39)	0.12	0.73	4.16	0.04	0.01	0.90
RAVLT total I-V (1)	52.20 (1.14)	52.48 (1.94)						
RAVLT total I-V (2)	49.33 (0.99)	48.24 (1.68)	0.001	0.97	17.42	0.00	0.05	0.83
RAVLT Del (R1)	10.52 (0.37)	10.90 (0.63)						
RAVLT Del (R2)	9.92 (0.36)	8.87 (0.61)	0.84	0.36	7.94	0.006	0.29	0.59
RAVLT list B (R1)	6.18 (0.26)	6.36 (0.43)						
RAVLT list B (R2)	6.22 (0.28)	6.46 (0.47)	0.10	0.75	6.72	0.01	0.24	0.62
Visual reprod. Imm.1	35.66 (0.51)	36.56 (0.85)						
Visual reprod. Imm.2	35.22 (0.47)	35.33 (0.78)	0.07	0.79	21.68	0.00	0.34	0.56
Visual reprod. Delay. 1	33.25 (0.69)	33.58 (1.15)						
Visual reprod. Delay. 2	33.73 (0.61)	32.52 (1.02)	3.61	0.06	25.95	0.00	0.16	0.69
RBMT story immed. 1	10.02 (0.39)	8.59 (0.65)						

	PSE (0,1) n=60 Mean (sd/se)	PSE (2+) n=20 Mean (sd/se)	EFFECT OF TIME F	P	NART F	P	GROUP F	P
RBMT story immed. 2	9.57 (0.44)	7.26 (0.74)	0.26	0.61	28.40	0.00	7.52	**0.008**
RBMT story delayed 1	8.81 (0.39)	7.72 (0.65)						
RBMT story delayed 2	8.30 (0.42)	6.97 (0.70)	0.00	1.00	23.17	0.00	3.25	0.08
RBMT standardised score 1	22.22 (0.29)	21.12 (0.50)						
RBMT standardised score 2	21.92 (0.29)	21.33 (0.50)	0.04	0.84	13.22	0.001	3.39	0.07

*Trails A and B were introduced at the second round of assessments and therefore no time effects or interactions could be measured. There were no significant time by NART or time by group interactions.

Table 8.8. CPT –IP Adjusted means presented

		PSE O,1 n=46 Mean (se)	PSE 2+ n=13 Mean (se)	Group F	P	Stimulus F	P	NART F	P	Distraction F	P	Significant group interactions
Log Randoms												
Fast Numbers	No distraction R1	0.47 (0.08)	0.38 (0.16)									Stimulus * round * group F=5.41 P=0.02
	No distraction R2	0.26 (0.09)	0.37 (0.16)									
	Distraction R1	0.60 (0.08)	0.88 (0.16)									
	Distraction R2	0.38 (0.10)	0.72 (0.19)	1.28	0.26	0.01	0.93	14.41	0.00	2.09	0.15	
Fast Shapes	No distraction R1	0.40 (0.09)	0.78 (0.16)									
	No distraction R2	0.39 (0.10)	0.31 (0.18)									
	Distraction R1	0.48 (0.10)	0.64 (0.19)									
	Distraction R2	0.42 (0.10)	0.62 (0.18)									
D Prime												
Fast Numbers	No distraction R1	1.73 (0.12)	1.50 (0.23)									Distraction *group F=3.99 P=0.05 Stimulus * round* group F=6.01 P=0.02
	No distraction R2	1.88 (0.11)	1.44 (0.21)									
	Distraction R1	1.91 (0.12)	1.83 (0.22)									
	Distraction R2	2.18 (0.12)	1.79 (0.23)	4.04	0.05	0.002	0.96	21.61	0.00	0.78	0.38	
Fast Shapes	No distraction R1	2.12 (0.12)	1.29 (0.23)									
	No distraction R2	2.48 (0.13)	2.08 (0.24)									
	Distraction R1	1.83 (0.08)	1.50 (0.15)									
	Distraction R2	2.26 (0.11)	2.04 (0.21)									
Log Beta												
Fast Numbers	No distraction R1	-0.25 (0.11)	-0.59 (0.20)									Distraction * group F=7.05 P=0.01
	No distraction R2	-0.06 (0.12)	-0.47 (0.23)									
	Distraction R1	-0.09 (0.11)	-0.06 (0.21)									
	Distraction R2	-0.02 (0.10)	-0.01 (0.20)	0.10	0.76	2.21	0.14	0.84	0.36	0.46	0.53	
Fast Shapes	No distraction R1	-0.31 (0.11)	-0.23 (0.21)									
	No distraction R2	0.03 (0.12)	-0.15 (0.24)									
	Distraction R1	-0.26 (0.13)	-0.11 (0.24)									
	Distraction R2	-0.14 (0.13)	0.10 (0.25)									

Table 8.9. CPT –IP Adjusted means presented

		PSE 0,1 n=46 Mean (se)	PSE 2+ n=13 Mean (se)	Group F	Group P	Stimulus F	Stimulus P	NART F	NART P	Speed F	Speed P	Significant group interactions
Log Randoms												
Numbers	Fast R1	0.47 (0.08)	0.38 (0.16)									Stimulus *
No distraction	Fast R2	0.26 (0.09)	0.37 (0.16)									speed * round
	Slow R1	0.39 (0.08)	0.47 (0.15)									* group
	Slow R2	0.30 (0.07)	0.18 (0.13)	0.55	0.46	3.11	0.08	15.91	0.00	1.35	0.25	F=6.09 **P=0.02**
Shapes	Fast R1	0.40 (0.09)	0.78 (0.16)									
No distraction	Fast R2	0.39 (0.10)	0.31 (0.18)									
	Slow R1	0.57 (0.09)	0.76 (0.15)									
	Slow R2	0.33 (0.09)	0.57 (0.18)									
D Prime												
Fast Numbers	Fast R1	1.91 (0.12)	1.83 (0.22)									Stimulus *
	Fast R2	2.18 (0.12)	1.79 (0.23)									round * group
	Slow R1	2.38 (0.13)	2.09 (0.25)									F=1.20
	Slow R2	2.43 (0.12)	1.82 (0.23)	2.68	0.11	0.36	0.59	22.36	0.00	0.68	0.41	**P=0.01**
Fast Shapes	Fast R1	1.83 (0.08)	1.50 (0.15)									
	Fast R2	2.26 (0.12)	2.04 (0.21)									
	Slow R1	2.44 (0.12)	2.04 (0.24)									
	Slow R2	2.63 (0.12)	2.47 (0.22)									
Log Beta												
Fast Numbers	Fast R1	-0.25 (0.11)	-0.59 (0.20)									Speed *
	Fast R2	-0.06 (0.12)	-0.47 (0.23)									group
	Slow R1	-0.20 (0.12)	-0.04 (0.23)									F=4.95
	Slow R2	-0.37 (0.14)	-0.20 (0.26)									P=0.03
Fast Shapes	Fast R1	-0.31 (0.11)	-0.23 (0.21)	0.08	0.78	1.08	0.30	1.36	0.25	2.19	0.14	
	Fast R2	0.03 (0.12)	-0.15 (0.24)									
	Slow R1	-0.25 (0.13)	-0.24 (0.25)									
	Slow R2	-0.19 (0.15)	-0.07 (0.28)									

8.4. Symptom change and neuropsychological performance (round 1 to round 2).

In order to examine any link between neuropsychological performance and developing psychosis, those HR participants who experienced an increase in psychotic symptoms (from study PSE score 0 or 1, to 2 or more) were compared with those who remained without psychotic symptoms (study PSE score 0 and 1) over the two assessments.

Five of the HR participants showed an increase in study PSE score from 0 or 1 to 2 or 3 between the first and second assessment, while 54, who had initially scores 0 or 1, continued to score in that range. The descriptive statistics for these two groups for all the variables are shown in Table 8.10. The NART scores for the two groups were comparable. However, the WAIS-R Full Scale IQ scores exhibited an interesting difference, 102.0 (13.2) for those without symptom change and 92.8 (6.8) for those with symptoms change, a difference of 9.2 IQ points. This difference was not due to any discrepancy between individual' WAIS-R PIQ and VIQ scores, both of which contribute to the WAIS-R FSIQ. There was a much greater NART minus WAIS-R FSIQ discrepancy for the symptom change group, indicating that those who developed a psychotic symptom during the study were already performing more poorly at baseline than pre-morbidly (NART). The mean NART – WAIS-R FSIQ discrepancy score was 10.6 (9.96) IQ points. This suggests that there is a decline in IQ even before the actual psychotic symptom develops. This would appear to be the most important finding here.

The means of for the two groups for the three outcome variables of the CPT-IP are presented in Table 8.11. The group with increasing symptoms exhibited a greater change in performance for the shape stimuli (both distracted and not) on all three outcome measures than the group with no symptoms change. Discriminability, as measured by d', was improved between the two assessment although the overall performance was not necessarily better. A greater change towards conservative responding, as measured by log beta, was observed although the increasing symptoms group was consistently more conservative. A greater decrease in responding to random stimuli, as measured by log randoms, was observed in the increasing symptoms group,

but again this group generally tended to respond more randomly. However, there was not such consistent change for the number stimuli over the two assessments. These results are tentative and should be treated with a high degree of caution as the group with increasing symptoms was very small (only 3 for CPT-IP measures) and differences between the groups in terms of degree of change were also small.

Table 8.10. Comparison of neuropsychological functioning in the 'without symptoms' and 'increase in symptoms' groups between the first and second round of assessments.

	No change in symptoms N=54 Mean (sd)		Change in symptoms N=5 Mean (sd)	
Baseline intellectual functioning				
VIQ	100.2 (12.1)		94.8 (7.8)	
PIQ	103.8 (14.4)		93.0 (11.0)	
FSIQ	102.0 (13.2)		92.8 (6.8)	
Block design	11.5 (3.0)		10.0 (4.0)	
	12.7 (3.0)	*1.2*	11.6 (4.2)	*1.6*
Premorbid intellectual functioning				
NART	100.0 (10.7)		103.4 (5.5)	
NART- WAIS-R Full Scale IQ difference	-2.15 (8.95)		10.60 (9.96)	
Executive function				
Stroop3	22.8 (5.4)		21.4 (3.0)	
	21.5 (4.6)	*1.2*	19.7 (3.0)	*-1.7*
Verbal fluency FAS total	39.0 (14.7)		34.0 (17.9)	
	40.7 (15.6)	*1.7*	38.0 (16.2)	*4.0*
	16.2 (5.2)		13.0 (4.4)	
Animals	15.9 (5.2)	*-0.3*	14.0 (4.2)	*1.0*
Hayling time A	17.2 (15.0, 19.9)		14.6 (7.5, 35.3)	
	14.2 (12.7, 15.9)	*-3.0*	17.3 (8.9, 41.0)	*2.7*
Hayling Total	5.0 (1.5, 17.0)		4.0 (0.5, 15.5)	
	3.0 (0, 7.0)		3.0 (0.5, 13.0)	
Perceptual motor speed				
Digit symbol	11.1 (3.0)		11.4 (2.4)	
	11.3 (3.0)	*0.2*	11.2 (2.0)	*-0.2*
Mental control / encoding				
WAIS-R Digits forwards	8.9 (2.3)		8.8 (2.8)	
	8.6 (2.5)	*-0.3*	10.2 (2.2)	*1.4*
WAIS-R Digits back	7.3 (2.4)		7.0 (3.0)	
	7.7 (2.4)	*0.4*	7.6 (2.9)	*0.6*
Verbal ability and language				
Token test	163 (162, 163)		162 (160.5, 163)	
	163 (162, 163)		163 (160.5, 163)	
Speed of comprehension	63.8 (18.9)		73.6 (8.7)	
	70.4 (19.0)	*6.6*	77.6 (16.2)	*4.0*
Spot the word	45.8 (5.7)	*1.6*	45.2 (2.9)	*-0.02*
	47.4 (4.8)		45.0 (2.5)	
Learning and memory				
Rey Auditory Verbal Learning Test				
Total 1-5	51.8 (9.3)	*-2.6*	53.6 (6.8)	*-6.0*
	49.2 (8.8)		47.6 (6.1)	
Delayed Recall	10.5 (2.9)	*-0.06*	10.4 (2.9)	*-1.8*
	9.9 (2.9)		8.6 (2.1)	
WMS-R Visual reproductions				
Immediate	35.9 (4.0)	*-0.40*	36.0 (5.1)	*-2.0*
	35.5 (3.6)		34.0 (4.8)	
Delayed	33.5 (6.3)	*0.40*	33.8 (6.1)	
	33.9 (4.6)		31.8 (7.6)	*-2.0*
Rivermead Behavioural Memory Test				
Standardised score	23.0 (21.0, 24.0)		21.0 (21.0, 23.0)	
	22.5 (20.25, 24.0)		23.0 (20.0, 23.5)	
Story Immediate recall	9.8 (2.9)	*-0.03*	9.6 (3.3)	*-1.7*
	9.5 (3.7)		7.9 (2.9)	
Story Delayed recall	8.6 (2.9)	*-0.2*	7.8 (2.2)	*0.0*
	8.4 (3.4)		7.8 (3.1)	

Table 8.11. Comparison of the CPT-IP between the 'without symptoms' and 'increase in symptoms' groups; first and second assessment.

	No change in symptoms Mean (sd) n=42		Increase in symptoms Mean (sd) n=3	
D prime				
Numbers non-distraction	1.9 (0.9)		2.2 (1.0)	
	2.2 (1.0)	*0.3*	2.5 (1.3)	*0.3*
Numbers distraction	1.7 (0.9)		2.1 (0.9)	
	1.9 (0.9)	*0.2*	1.9 (1.1)	*-0.2*
Shapes non-distraction	1.9 (0.7)		1.7 (0.2)	
	2.3 (0.8)	*0.4*	2.7 (0.9)	*1.0*
Shapes distraction	2.2 (1.0)		1.2 (1.0)	
	2.5 (0.9)	*0.3*	2.0 (0.9)	*0.8*
Ln Beta				
Numbers non-distraction	-0.3 (0.7)		-0.6 (1.2)	
	-0.1 (0.8)	*0.2*	-0.5 (0.6)	*0.1*
Numbers distraction	-0.1 (0.8)		-0.7 (1.1)	
	-0.1 (0.7)	*0.0*	-0.6 (1.1)	*0.1*
Shapes non-distraction	-0.4 (0.8)		-0.4 (0.6)	
	-0.1 (0.8)	*0.3*	-1.0 (0.3)	*-0.6*
Shapes distraction	-0.3 (0.9)		0.3 (1.0)	
	-0.2 (0.9)	*0.1*	-0.4 (0.5)	*-0.7*
Ln Randoms				
Numbers non-distraction	0.5 (0.7)		0.5 (0.4)	
	0.3 (0.6)	*-0.2*	0.2 (0.4)	*-0.3*
Numbers distraction	0.6 (0.6)		0.6 (0.6)	
	0.4 (0.7)	*-0.2*	0.8 (0.8)	*0.2*
Shapes non-distraction	0.4 (0.5)		0.9 (0.8)	
	0.4 (0.7)	*0.0*	0.2 (0.4)	*-0.7*
Shapes distraction	0.5 (0.7)		(1.1)	
	0.4 (0.7)	*-0.1*	0.7 (0.7)	*-0.4*

Note: d' = attentional capacity; ln beta = response bias or tendency to over- or under-respond; ln randoms = tendency to respond to random stimuli. Figures in italics represent differences between the means of the first and second round assessment for individual variables.

8.4.1. Summary of neuropsychological findings

The purpose of the above analysis was to investigate whether the presence of symptoms at baseline and ever (including the 10 with a diagnosis of schizophrenia who were assessed prior to the manifestation of the illness) resulted in significantly reduced neuropsychological assessment scores at baseline and follow-up compared to those who remained asymptomatic. The findings are provisional and may change over time as more subjects become ill. In addition a concern was to investigate whether between

group differences (suggesting the HR performance to be poorer than controls in some situations) could simply be due to the reduced performance of the symptom positive group. Univariate and multivariate analyses were conducted and 2 categories of symptom classification were employed, symptoms at baseline and symptoms ever. The effect of symptoms on change over time was evaluated. Change in symptoms between round one and round two was examined. The presence of symptoms appeared to affect neuropsychological functioning, particularly memory and verbal performance, by reducing scores in some areas. However, when symptoms were controlled in the statistical analyses group differences remained suggesting that while important, symptoms do not account for all group differences. Analysing the composite scores, symptoms had a significant effect on mental control/encoding, perceptual motor speed, learning and memory and a trend towards an effect for language functioning. Also symptoms ever was associated with significantly greater NART /WAIS-R FSIQ discrepancies suggesting a reduction in functioning from premorbid levels, this discrepancy was seen in those who were asymptomatic at baseline assessment but who developed symptoms later (n=5), indicating that the decline in intellectual functioning had begun prior to the onset of symptoms. A reduction in memory functioning (reduced RBMT standardised scores) and attention capacity and a more cautious response style on the CPT-IP were evident in the symptoms ever group when the across time analyses was conducted.

The neuropsychological decline associated with the presence of symptoms may in fact, have begun prior to the onset of the symptoms, indicating that some mechanism may be operating prior to the onset of symptoms to reduce the individuals cognitive functioning. Difficulties with memory and attention appear to be associated with the presence of symptoms.

8.5. Breakdown of the socio-demographic variables by symptoms (ever rated)

From Table 8.12 it is very clear that subjects who had a study PSE symptom score of 2 or more (including the 10 subjects with a study PSE 4 rating), had more deviant developmental histories than those without such symptoms. This includes significantly

more psychological problems, missed more school, had a greater number of forensic contacts, more social work involvement, had been more often in foster care, were unemployed, and in the past and at baseline assessment, used drugs more frequently than those without symptoms.

Table 8.12. Breakdown of the socio-demographic variables by symptoms (ever rated)

	High Risk PSE (0/1) N=108 %	High Risk PSE (2+) N=47 %	Controls PSE (0/1) N=32 %	χ^2,	df	p
No past cannabis	46	34	41	15	4	**0.006**
Extreme cannabis	7	23*	0			
No current cannabis	71	60	84	11	4	**0.03**
Extreme cannabis	6	17*	0			
No other drugs past	66	47	66	7	4	NS
Extreme past other	6	15	6.3			
No other drugs current use	85	68	94	12	4	**0.02**
Occasional current	10	28*	6			
Extreme Past and current alcohol	23	19	22	2	4	NS
Reading problems	16	21	9	3	2	NS
Dyslexia[#]	1	6	0			
Residential school	4	4	3	1	2	NS
Speech and language problems	16	9	16	1	2	NS
Missed School	15	32*	19	13	2	**0.001**
Psychological problems	31	48*	13	12	2	**0.002**
Forensic contacts	19	45*	16	15	2	**0.001**
Children's panel appearances[&]	12	23*	3			
Social work involvement	26	44	9*	8	2	**0.02**
In care/ fostered/ adopted	7	15*	0	6	2	**0.06**
Unemployed	11	32*	9	19	4	**0.001**

[#]No statistics were calculated due expected values in many cells being less than 5%

[&]This variable had 4 categories representing different reasons for appearance before the children's panel. These included social work involvement in the family and issues relating to child-care and fostering, and appearances for behavioural disturbances, truancy, and a category 'other'. Although the overall chi-square value was not significant, there was an adjusted standardised residual of 2.5 for 'other behavioural problems' for the HR PSE positive group who had a rate of 11%, compared to 3% in the HR PSE negative group, and 0% in the control group.

8.8 Discussion

The baseline univariate analysis revealed significant differences between the HR subjects who had no study PSE rated psychotic symptoms and those who had, for FAS (although the finding was in the opposite direction to that expected, with higher scores in the study PSE positive group), vocabulary subtest of the WAIS-R, RBMT immediate story recall, and trends for Spot the Word, SCOLP, and the RBMT story delayed recall.

When the variable PSE 'symptoms ever' rated was used, significant differences were found between the symptom groups for FAS, RBMT story immediate recall and delayed recall, and trends for vocabulary, and RBMT standardised scores.

When an analysis was conducted on the factor scores, the PSE positive group were poorer than the PSE negative group for factor 3 (comprising the story immediate and delayed recall, and time to complete HSCT). In the analysis of the adjusted composite scores, the PSE positive group had significantly poorer scores than the PSE negative group on perceptual motor speed, and there was a trend for this finding on the learning and memory composite.

The analysis outlined in section 8.2.5 was an investigation into the degree to which the group differences at baseline, as outlined in Chapter 5, could be explained by the presence of symptoms. For this analysis, only the adjusted composite scores were analysed to reduce the number of analyses. The results suggested that comparing the controls, the HR group and the Patients, and controlling for symptoms, group differences remained between the groups on the learning and memory composite and when the variable 'symptoms ever' was used to define symptom presence, the HR and controls were found to be significantly different on the composite of learning and memory , but the HR and patient groups were indistinguishable.

Symptoms had a significant effect on mental control/encoding and perceptual motor speed. When 'symptoms ever' were included (including those with PSE 4), symptoms were found to also have a significant effect on learning and memory.

These findings are indeed intriguing and they suggest that the presence of symptoms may have a damaging effect on memory but that even when the symptoms are controlled in the analysis and the three groups are compared, significant differences between the groups remained for learning and memory measures.

Executive measures of HSCT did not appear to be in anyway associated with the presence of symptoms and it could mean that it is a marker of the general genetic vulnerability. Memory appears also to be a characteristic of the risk group generally, but it appears to decline in the presence of symptoms suggesting that the presence of symptoms is accompanied by a deterioration of an already impaired function.

In section 8.3, change over time was examined. The baseline IQ data indicated significantly poorer current IQ scores but not lower NART, in the PSE positive group compared to the PSE negative group. A significant deterioration from pre-morbid levels of functioning was noted in the PSE positive group. Overall, the PSE positive group showed the same deficits at follow-up as they did at baseline, confirming the results of the baseline analyses, and indicating the finding to be stable. The absence of a significant effect of time indicates that little change occurred between time one and time two, and therefore little deterioration occurred over time.

The important, and most interpretable finding with regard to the CPT-IP was that D prime was reduced in the PSE positive group. Lower D prime values have been reported in relatives of patients with schizophrenia and are thought to be possible markers for schizophrenia (Cornblatt and Keilp, 1984). Lower D prime scores have been observed in symptomatic relatives also. Steinhauer et al., (1991) found D prime scores on a degraded visual version of the CPT to be lower in the brothers of patients with schizophrenia, who themselves had diagnoses of schizophrenia spectrum disorders, compared to brothers with no diagnoses. Mirsky et al., (1995) from the Roscommon study reported that an attentional deficit was shared, albeit to a lesser extent, by those relatives who also had a DSM-III-R diagnosis (56%) compared to those without a diagnosis, who were indistinguishable from controls. These findings

challenge the suggestion by Cornblatt et al, (1997), that 'impaired attention clearly reflects a biologically based abnormality that is independent of clinical symptoms prior to the onset of illness'.

The CPT-IP deficit in those with, compared to those without symptoms is very interesting. It may be that measures of attention deficits are associated with the development of schizophrenia, but it is really too early to say. Erlenmeyer-Kimling and Cornblatt (1987) reported lower signal/noise disturbance on a memory load CPT at age 7-12 among HR subjects to be predictive of hospitalisation or psychiatric treatment in late adolescence, these children were the sole source of the CPT deficits at 7-12.

Between the baseline and first follow-up assessment, 5 subjects developed psychotic symptoms. This afforded us a unique opportunity to study the neuropsychological changes associated with the development of symptoms. As there are only 5 subjects the use of statistical analyses may be questionable. These five subjects exhibited a reduction in current IQ measures from premorbid levels. This suggests that even at baseline, prior to the onset of any symptoms, a decline in intellectual functioning had already begun, at least 18 months prior to the follow-up assessment. This is an interesting result in light of the work of Professor Hafner (Hafner et al., 1998) and colleagues who have found that decline in social and decline in general functioning can begin as much as 6 years prior to the onset of symptoms in patients with schizophrenia.

Many studies have indicated that IQ is a risk factor for the development of schizophrenia (Aylward et al., 1984). In this group the decline in IQ is important, as it was not the case that these 5 subjects always had lower IQ (of course it must be remembered that these 5 subjects do not have schizophrenia, but PSE positive symptoms and in the end, the importance of these findings may change, this interpretation must be viewed tentatively).

It was noted by Kremen et al., (1998), that in 10% of individuals with substantially larger than expected IQ declines from age 4-7, the rate of psychotic symptoms at age 23 was nearly 7 times as high as for others. They noted it was specific to psychotic

symptoms but not schizophrenia. While we do not have childhood data, the onset of the decline in IQ cannot be accurately dated, but to achieve reasonable scores on the NART, some degree of educational attainment is necessary, for this reason the decline in IQ probably occurred fairly recently (to baseline assessment) at least in the early adult years, as if the decline occurred in childhood then the NART might be expected to be lower. In addition to the IQ decline in these 5 subjects they tended to have lower scores in other domains which is predictable given the decline in general current intellectual functioning.

The HSCT time to complete section A was increased in the group from quite a fast baseline level, which could indicate regression to the mean or indeed a slowing down of cognitive processing. Scores for the story immediate recall were reduced at the second compared to the baseline assessment.

At this time it is difficult to draw any firm conclusions other than a decline in IQ from estimated premorbid levels has occurred in conjunction with the development of psychotic symptoms, also this was accompanied by the reduction in scores in some other areas of function. From Table 8.12 it is very clear and very unlikely to be just a chance finding, that those subjects within the HR group who have symptoms (including the 10 subjects with a PSE 4 rating) compared to those without, and to controls, demonstrate marked deviant patterns of development. These included increased numbers of previous psychological problems, missed school, forensic contacts, social work involvement, unemployment, and foster care. Of particular interest is the increase in the rates of current and past drug usage in these subjects. What is not clear is: - whether such drug usage is the cause of psychotic symptoms, at least in some individuals, and perhaps if this habit was ceased then the symptoms may disappear; - whether such drug usage is the cause of psychotic symptoms, and has operated through an interaction with the genetic predisposition to schizophrenia; -whether the presence of psychotic symptoms has led subjects to take drugs, as some sort of self medication phenomenon. The latter explanation is unlikely given that subjects saw themselves as well and did not complain about symptoms, however it is also possible that they are trying to hide them from the psychiatrist. It is not the case that these differences were

caused solely by the 10 subjects with study PSE 4 ratings. It is not possible to say but in time, a detailed path analysis can be constructed to examine the nature of the relationships between the socio-demographic variables and the presence of symptoms, and more specifically the development of schizophrenia. At the present time, it is not possible to say exactly what these symptoms mean, perhaps in time they will disappear in some subjects. However it is likely that once a psychotic symptom has been present, the individual at least has the propensity for psychotic symptoms, even if they are not always present, and this may signify that they are fundamentally different to subjects who never experience psychotic symptoms.

In summary, the presence of study PSE psychotic symptoms, in the HR group generally, are accompanied by difficulties, particularly in the area of memory and may be accompanied by poorer ability to sustain attention. Also a decline in IQ before the onset of symptoms is likely. However, all of these results must be seen as preliminary as the development of symptoms is a changing story in the HR group as they pass through the risk period.

Chapter Nine: Neuropsychological assessment results, PSE symptoms, and socio-demographic details, according to family history of psychosis

9.1. Introduction

In this chapter the degree to which genetic liability affects the neuropsychological test results, the symptom ratings, and socio-demographic variables, is assessed.

9.2. Categorical definition of family history of psychosis

Family history for psychiatric disorder was coded in two ways, categorically and quantitatively. The categorical coding was created by making 4 categories of family history, including, no family history (controls), two second degree relatives only, one first degree relative and at least one other 2nd degree relative, and the fourth category included all those with at least two 1st degree relatives. These categories were somewhat arbitrary, but took account of the degree of morbid risk associated with closeness of relationship to an individual with schizophrenia as estimated from family, twin, and adoption studies (Gottesman and Shields, 1982; outlined in chapter 1, Table 1.1). A quantitative measure of genetic risk was applied to the high-risk group only. The method of calculating the quantitative risk was devised by Dr. Pak Sham, Reader in Psychiatric and Statistical Genetics at the Institute of Psychiatry, London, who kindly helped us in our endeavours. The calculation of the risk variable is outlined in Appendix 4, 9.1.

Estimates of quantitative liabilities were calculated for each person within the high-risk group only. A histogram of the genetic liabilities for the total HR group is presented in figure 9.1. A histogram of the quantitative genetic liabilities for those with second degree relatives affected (at least two) is given in figure 9.2. A similar histogram for those with one first degree relative and at least one second degree relative, is given in figure 9.3. For those with at least 2 first degree relatives affected the histogram of genetic liabilities is given in Figure 9.4. It is evident from the histogram of the genetic liabilities for the total group shown figure 9.1 that the distribution of genetic liabilities is distinctly bi-modal in the groups. The range of genetic liabilities by specific family history categories is given in Table 9.1.

Table 9.1. Range of genetic liabilities for specific family history

Family history categories	Range of quantitative genetic liabilities
Mother/father, and sibling	0.37219 to 0.61320
Mother and second degree relative	0.31275 to 0.56289
Father and second degree relative	0.32999 to 0.61462
Two siblings	0.30739 to 0.40978
One sibling	0.10484 to 0.26848
Second degree relatives only	-0.16870 to 0.10484

Figure 9.1. Histogram of Genetic Liabilities for the High Risk Group; Total

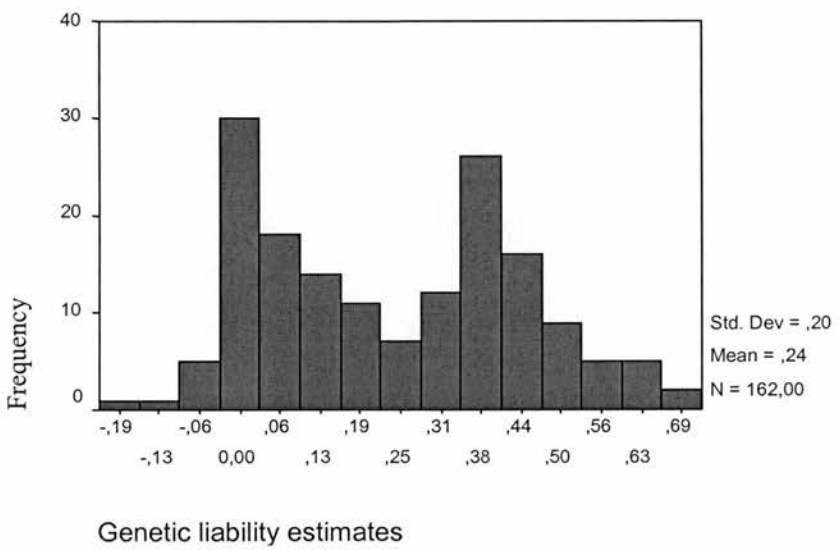


Figure 9.1. Histogram of genetic liabilities for the high-risk group

Figure 9.2. Genetic liabilities of those with affected second degree relatives only

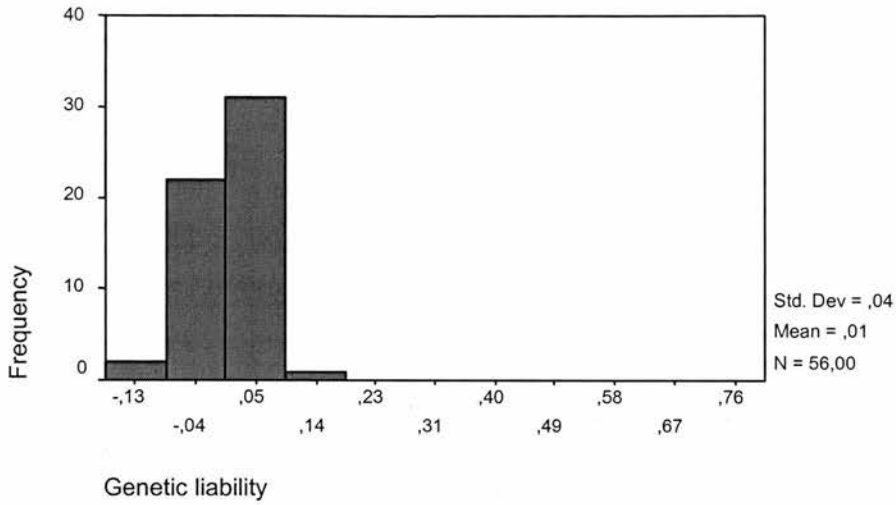


Figure 9.2. Histogram of genetic liabilities for those with affected second degree relatives

For figure 9.2 the genetic liability estimates for those with two or more second degree relatives ranged from –0.16870 to 0.10484..

Figure 9.3. Histogram of Genetic Liabilities for those with at least one first degree relative

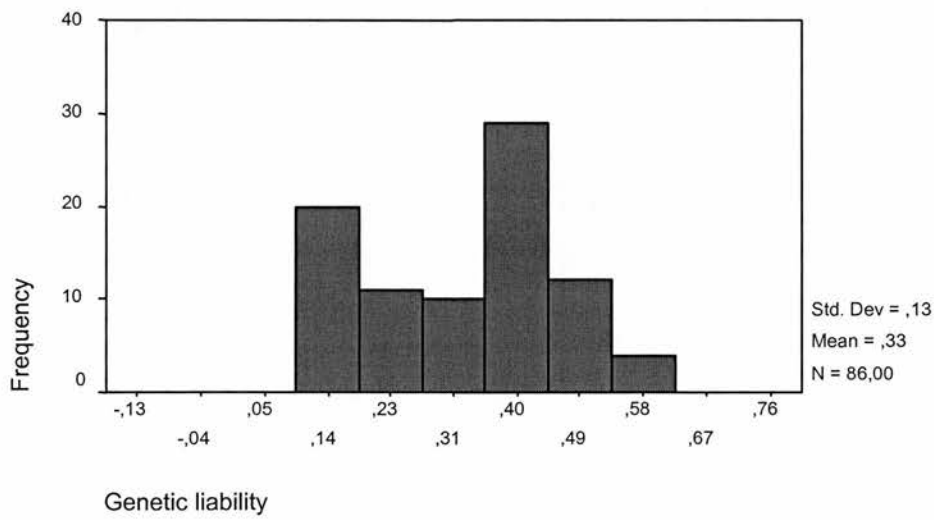


Figure 9.3. Histogram of genetic liabilities for those with at least one first degree relative affected

As shown in Figure 9.3 the genetic liability estimates for those with one first degree relative and at least one second degree relative ranged from 0.10484 to 0.61462.

Figure 9.4. Histogram of Genetic Liabilities for those with at least 2 first degree relatives

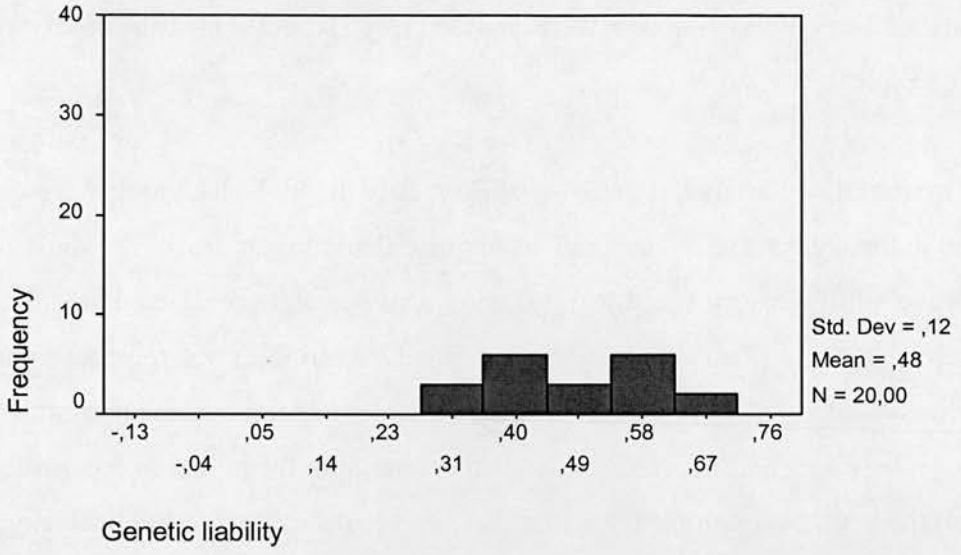


Figure 9.4. Histogram of genetic liabilities for those with at least 2 affected first degree relatives

As shown in Figure 9.4 the genetic liability estimates for those with more than one first degree relative ranged from 0.30739 to 0.70465.

9.3. Statistical analyses of the neuropsychological data

Only those neuropsychological variables that distinguished the controls from the high-risk group, at baseline assessment or follow-up, were further analysed according to family history of schizophrenia, to see if the differences could be explained by genetic factors. The data were analysed using both definitions of family history for schizophrenia, the categorical and quantitative methods, as outlined above. For the categorical definition of family history, analysis of variance and analysis of co-variance were conducted on the baseline data, with NART as a co-variate were appropriate (Table 9.2). This analysis included the controls (family history =0). For the categorical variable controls were compared to the three categories of family history within the

high-risk group. All significant group main effects, for the model with NART as a co-variate, were examined using least squares difference based on the marginal means. Where NART was not used as a co-variate in the model (in situations were the variable was too similar to the NART e.g. WAIS-R measures, or for factors and composites including such variables) post hoc Scheffe tests were conducted to examine significant group main effects. Follow-up data were analysed using repeated measures analyses of variance (Table 9.3).

For the quantitative variable of genetic liability, only the high-risk group were included in the analysis as a measure was not calculated for controls. For the quantitative family history variable, regression analyses were conducted, and the quantitative measure of genetic liability (independent variable) was regressed onto the neuropsychological variables (dependent variables), in univariate regression models. Where appropriate, NART was also entered into the model to control for its effect on the neuropsychological test scores. The results of the models analysing baseline scores are given in Table 9.4. The results of the models are presented without controlling for NART by Genetic liability interactions. The interaction was tested in all models but did not improve the model, or change the results in any significant way. For the repeat assessments, the difference scores (scores at time one minus scores at time two) were entered as the dependent variables, and NART (where appropriate) and genetic liability were then entered as co-variates, it was felt that this would help to reduce the number of parameter in the models and increase the power. The results of the models analysing the repeat assessment data are given in Table 9.5.

9.3.1. Neuropsychological assessment results analysed by family history categories

The results of the analysis of the categorical definition of family history are outlined in Table 9.2, for the baseline data, and in Table 9.3 for the repeated assessments. From Table 9.2 it can be seen that many group differences existed between the family history groups. For the IQ variables the control group (Fhx=0) performed significantly better than the HR group. On VIQ the controls were significantly

different from Fhx1 (second degree relatives only) and Fhx2 (those with one 1st degree relative and second degree relatives) but not Fhx3 (2 or more 1st degree relatives). In terms of PIQ, the controls were significantly different to Fhx2. For FSIQ the controls performed significantly better than the other 3 family history groups. However there were no significant differences between any of the family history groups within the high-risk group for any IQ measure. The controls performed significantly better than Fhx2 and Fhx3 on block design. For the Hayling total error scores, the controls performed significantly better, making less errors, than Fhx3, also Fhx1 performed better than Fhx3, who had the highest rank scores on this test. When Hayling errors were examined more closely in terms of type A errors (correct completion of the sentence, when an incorrect response is required), the controls performed better than Fhx3, but also Fhx1 and Fhx2 made significantly less errors than Fhx3. For errors B (completion of the sentence with a word not entirely unrelated to the sentence), only significantly differences were found between the controls and Fhx2 and Fhx3. No significant differences existed between any of the family history groups in terms of RBMT standardised scores, or for the story, immediate recall. For the delayed story recall, the controls differed significantly from Fhx2 and Fhx3. No significant group differences were observed for any measure of the RAVLT, or for the verbal fluency measure, recall of animal names. For the composite memory score (description of how the composite scores were derived was outlined in chapter 4) the controls performed significantly better than Fhx2 and Fhx3, but not Fhx1. For factor two (factor analyses also described in chapter 4) which is a measure of performance/spatial ability, the controls had significantly higher factor scores than Fhx2 and Fhx3, in addition Fhx1 had significantly higher factor scores than Fhx2. Factor 2 was also analysed without NART as a co-variate as it is primarily composed of IQ measures and it was thought appropriate to analyse it both ways. In this analysis post hoc Scheffe tests revealed that controls had higher scores than Fhx2 but also that Fhx1 had significantly higher factor scores than Fhx2.

The results of the repeat analyses, round one to round two, are presented in Table 9.3. There was a significant effect of genetic liability for the RBMT total

standardised score, and a trend towards a difference for Hayling errors A. As the trend suggested group differences for the HSCT errors A the differences between the marginal means was investigated. Based on the marginal means, the controls (Fhx 0), had a significantly lower error score than Fhx 3 (2+ second degree relatives) and those with 2nd degree relatives only (Fhx1) had lower scores than those Fhx 3. In terms of the RBMT standardised score, the controls (Fhx 0) had significantly higher total scores than Fhx 2. There was a trend for the controls (p=0.06) and Fhx 1 (p=0.08) to have higher scores than Fhx3.

Significant time by group, interactions were found for HSCT errors total, errors A, errors B, and for the story immediate and delayed recall. For all HSCT variables all groups had reductions in errors over time but these were more marked for Fhx 2 and Fhx 3. For the story immediate recall of the RBMT the number of items remembered, decreased in all groups except for Fhx 2, where there was a slight increase. For the story, delayed recall, the controls and Fhx 2 had slight increases in scores while Fhx 1 and Fhx 3 scores decreased.

9.3.2. Regression analysis of the quantitative measure of genetic liability and neuropsychological assessment scores.

The results of the regression analysis for the baseline assessments are presented in Table 9.4. The overall significance of the model is presented along with the regression co-efficient for the effect of genetic liability, and for NART, where included in the model. The R^2 values for each model are also given. NART was not included in the models relating the quantitative variable to the IQ variables. There was no significant model and no significant effect of genetic liability suggesting that genetic liability measure is not related to the IQ measures. This was also confirmed by the very low R^2 values for the models. For the Hayling total error scores, errors A and errors B, there was no significant regression co-efficient for NART. For Hayling errors, type A, there was a significant (p=0.04) co-efficient for genetic liability, although the overall model was not significant. Where the dependent variable was not normally distributed both the dependent and independent variables were ranked and the regression analysis was conducted on the ranks (Kleinbaum et al., 1998), this

was done for all Hayling measures. There was no other association between Hayling error scores and genetic liability. For the rest of the analyses, there was only a trend ($p=0.06$) towards a significant effect of genetic liability on factor 2, when NART was included. When the analysis was conducted in the absence of NART this effect became significant ($p=0.03$) with a negative co-efficient –2.14, suggesting that an increase in genetic liability is associated with a reduction in factor scores for factor 2. The effect of genetic liability was not significant for the memory tests or for digit symbol.

In Table 9.5 the results of the regression of genetic liability on the difference scores (round 1- round 2) for the neuropsychological variables that distinguished the HR and control groups. For Hayling errors, type A, there was a significant effect for genetic liability ($p=0.04$), but the overall model was not significant. There was a significant effect of genetic liability for both the story immediate and delayed conditions. The dependent variable was scores for the round one story minus those for the second round story. This difference seems to differ as a function of genetic liability. Genetic liability did not relate to RBMT story at baseline. The co-efficient was negative in both cases suggesting an inverse relationship between genetic liability and difference scores, so that as the genetic liability scores rises the difference scores get smaller. The overall models for both story immediate and story delayed, were significant. When these differences were looked at more closely, it appeared that for those at higher risk performance remained more stable across rounds one and two compared to those at lower risk, who's performance on the story recall was higher initially but reduced more at second assessment. A more complex model was constructed to investigate this interaction. A repeated measures analysis of variance was conducted, with actual scores at time one and time two (as opposed to simply the difference scores) as within subject variables and NART and genetic liability as co-variates. The model confirmed a significant ($p=0.006$) time by genetic liability interaction for story immediate and story delayed, although the overall model was not significant and the main effects for genetic liability and time were not significant. The effect of genetic liability for all from the repeated measures analyses

of variance models is given in the final column of Table 9.5. No significant effects were observed but a trend was noted for RAVLT trial 1 and HSCT errors A.

Although the continuous performance test did not distinguish the high-risk group from controls at baseline or follow-up, the effect of genetic liability on CPT-IP performance was investigated. It was thought appropriate to do this analysis given the weighty literature suggesting that poor performance on the CPT-IP may be a biological marker for schizophrenia (Cornblatt and Obuchowski, 1997). The quantitative measure of genetic liability did not significantly correlate (Spearman's rank order correlations) with any of the CPT-IP measures. A multiple regression analysis was conducted in SPSS with the CPT-IP measures as dependent measures and genetic liability and NART as independent variables. The variation in the CPT-IP scores was not significantly explained by the variation in genetic liability, as expected from the non-significant correlations, there was a significant effect of NART for log randoms and d prime measures but not for the log beta measures. Also there were no significant differences across family history groups in terms of CPT-IP measures when the categorical description of family history was used.

9.3.3. Summary

While the baseline neuropsychological assessment data outlined in chapter 5 confirmed that for many areas of functioning there were differences between the controls and the HR group, in this chapter the primary interest was finding within HR group differences on these tests due to differences in genetic liability. While the HR versus control group differences were confirmed and outlined in Tables 9.2 and 9.3 also differences within the HR group were found to be associated with differing liability. From the baseline analyses presented in 9.2 for the categorical definition of family history within HR group differences were found for the Hayling total error scores, errors type A, and for factor_2. For the baseline assessments using the quantitative measure, results presented in Table 9.4, differences were found for Hayling errors A and factor_2. For the repeat analyses, using the categorical definition of family history, differences were found for RBMT standardised score and a trend for HSCT errors A (Table 9.3). For the quantitative measure of genetic

liability the differences were found for the difference scores (time1 to time 2) Hayling total errors, story immediate, and story delayed recall (Table 9.5). Also a trend was noted for an effect of genetic liability in the follow-up analyses for HSCT A and RAVLT trial 1. The overall indication is that both definitions of family history yield similar results. Higher risk appears to be associated with difficulties on the HSCT, and poorer spatial/performance ability (factor_2), and on the learning and memory composite. There is some indication that memory for meaningful verbal material, and changes over time in responses on such material may be related to genetic loading.

Table 9.2. Baseline neuropsychological variables analysed by family history for schizophrenia categories

Variable	No Family history of schizophrenia. Controls N=36, Fhx0 Mean (s.e.)	At least two second degree relatives affected N=56, Fhx1 Mean (s.e.)	One first degree relative and second degree relative affected N=86, Fhx2 Mean (s.e.)	Two first degree relatives affected N=20, Fhx3 Mean (s.e.)	Group effect F	 P	Effect of the co-variate, NART F	 P	Contrasts*
Verbal IQ	102.85 (2.03)	97.21 (1.64)	96.07 (1.27)	97.47 (2.71)	2.73	0.04			0≠1, 0≠2
Performance IQ	107.68 (2.49)	102.15 (2.02)	98.34 (1.57)	100.05 (3.34)	3.47	0.02			0≠2
Full Scale IQ	105.47 (2.24)	99.52 (1.81)	96.56 (1.41)	98.47 (3.00)	3.80	0.01			0≠1, 0≠2, 0≠3
NART	105.23 (1.64)	99.00 (1.36)	97.05 (1.05)	102.25 (2.13)	6.51	0.00			0≠1, 0≠2
NART-FSIQ	-0.23 (2.04)	-1.92 (1.70)	0.24 (1.30)	4.00 (2.66)	1.20	0.31			
Block design	12.47 (0.47)	11.58(0.38)	10.80 (0.29)	10.93 (0.61)	3.28	0.02	31.68	0.00	0≠2, 0≠3
HSCT total errors	97.32 (10.82)	97.15 (8.79)	109.93 (6.83)	135.92 (13.64)	2.27	0.08	1.29	0.26	0≠3, 1≠3
HSCT errors A	104.31 (10.12)	94.56 (8.22)	108.98 (6.38)	135.78 (12.75)	2.53	0.059	0.60	0.44	0≠3, 1≠3, 2≠3
HSCT errors B	84.23 (10.75)	106.60 (8.74)	112.05 (6.79)	133.07 (13.55)	2.91	0.04	0.74	0.39	0≠2, 0≠3
RBMT total	121.56 (9.74)	111.76 (7.91)	99.13 (6.12)	107.83 (12.61)	1.89	0.13	1.19	0.28	
Story immediate	10.17 (0.56)	9.54 (0.46)	8.92 (0.35)	8.77 (0.73)	1.43	0.24	28.39	0.000	
Story delayed	9.33 (0.52)	8.66 (0.43)	7.67 (0.33)	7.39 (0.67)	3.21	0.02	30.20	0.00	0≠3, 0≠2
RAVLT trial 1	7.07 (0.33)	6.10 (0.27)	6.50 (0.21)	6.57 (0.42)	1.77	0.15	7.59	0.006	
RAVLT total I-V	53.22 (1.42)	51.87 (1.17)	51.69 (0.91)	49.27 (1.85)	0.97	0.41	27.91	0.000	
RAVLT delayed recall	11.42 (0.46)	10.86 (0.38)	10.45 (0.30)	10.25 (0.59)	1.27	0.29	14.39	0.00	
Animals	17.23 (0.86)	16.37 (0.70)	15.33 (0.54)	14.58 (1.10)	1.57	0.20	11.56	0.001	
ADJ learning and mem. composite	0.05 (0.12)	-0.22 (0.10)	-0.46 (0.08)	-0.52 (0.15)	4.52	0.004			0≠2, 0≠3
Factor _2	0.39 (0.17)	0.22 (0.13)	-0.21 (0.11)	-0.22 (0.21)	4.29	0.006	9.85	0.002	0≠2, 0≠3, 1≠2
Factor_2 &	0.52 (0.16)	0.24 (0.13)	-0.27 (0.11)	-0.16 (0.21)	6.61	0.00			0≠2, 1≠2 0≠2, 0≠3, 1≠2
Digit symbol	10.73 (0.45)	9.96 (0.36)	10.07 (0.28)	10.10 (0.57)	0.67	0.57	23.82	0.00	

*All significant group main effects, for the model with NART as a co-variate, were examined using least squares difference based on the marginal means. Where NART was not used as a co-variate in the model, post hoc Scheffe tests were conducted to examine group significant main effects. &NART not in model

Table 9.3. Neuropsychological variables, follow-up data, analysed by family history for schizophrenia categories

Variable		Fhx0 Mean (s.e)/ Median (25th, 75th Percentile N=22	Fhx1 Mean (s.e)/ Median (25th, 75th percentile N=23	Fhx2 Mean (s.e)/ Median (25th, 75th percentile N=50	Fhx3 Mean (s.e)/ Median (25th, 75th percentile N=7	Group# F	Group# P	NART F	NART P	Time F	Time P	Time by Group F	Time by Group P
HSCT total errors	1	3 (1, 5)	2 (0.75, 7)	7 (1, 19)	12 (5, 19)	2.07	0.11	0.64	0.43	31.42	0.00	3.47	0.02
	2	1 (0.5, 3.5)	2 (0, 5.5)	2 (0, 6)	1 (1, 7)								
HSCT errors A	1	3 (0, 3)	0 (0, 6)	3 (0, 10)	3 (3, 10)	2.43	**0.07**¤	0.11	0.74	24.35	0.00	4.15	0.01
	2	0 (0, 1.5)	0 (0, 3)	0 (0, 3)	0 (0, 6)								
HSCT errors B	1	0.5 (0, 2)	1.5 (0.75, 3.25)	2 (0.5, 11.5)	3 (2, 9)	1.90	0.13	0.15	0.70	15.46	0.00	2.86	0.04
	2	1 (0, 1.5)	1 (0, 2.25)	1 (0, 3.5)	1 (1, 1)								
Block design	1	13.00 (0.62)	11.76 (0.63)	10.97 (0.43)	12.93 (1.05)	1.96	0.13	10.80	0.00	0.54	0.46	0.98	0.40
	2	13.61 (0.64)	12.79 (0.66)	12.30 (0.44)	13.70 (1.09)								
RBMT total	1	24 (22, 24)	23 (22, 24)	22 (20, 24)	23 (18, 24)	2.76	**0.05***	6.76	0.01	20.50	0.00	0.49	0.69
	2	23 (21, 24)	23 (21, 24)	22 (20, 23)	20 (20, 23)								
Story immediate	1	11.29 (0.64)	10.70 (0.65)	9.58 (0.42)	9.47 (1.08)	1.44	0.24	30-98	0.00	0.66	0.42	3.41	0.02
	2	10.44 (0.74)	8.15 (0.76)	9.74 (0.49)	8.54 (1.26)								
Story delayed	1	10.19 (0.62)	10.02 (0.63)	8.24 (0.41)	8.38 (1.04)	3.02	0.34	26.94	0.00	0.26	0.61	3.03	0.03
	2	10.31 (0.70)	7.85 (0.72)	8.41 (0.46)	7.34 (1.19)								
RAVLT trial 1	1	7.37 (0.43)	6.27 (0.43)	6.94 (0.28)	6.94 (0.73)	0.82	0.48	7.01	0.01	0.03	0.87	1.79	0.25
	2	5.36 (0.38)	5.55 (0.37)	6.07 (0.25)	5.29 (0.64)								
RAVLT trials I-V	1	54.62 (1.86)	54.49 (1.86)	52.79 (1.23)	47.58 (3.16)	1.10	0.35	21.05	0.00	0.04	0.85	1.01	0.39
	2	49.33 (1.65)	49.41 (1.65)	50.06 (1.09)	46.09 (2.80)								
RAVLT delayed	1	12.04 (0.59)	11.38 (0.59)	10.56 (0.39)	9.76 (1.01)	1.61	0.19	8.01	0.01	0.88	0.35	0.85	0.47
	2	10.57 (0.59)	9.71 (0.59)	9 87 (0.39)	9.11 (1.00)								
Animals#	1	18.12 (1.30)	16.43 (1.30)	15.78 (0.84)	13.99 (2.32)	1.17	0.18	10.14	0.01	0.01	0.93	0.03	0.82
	2	18.28 (1.08)	16.54 (1.07)	15.37 (0.69)	15.47 (1.91)								
Digit symbol	1	11.47 (0.64)	10.79 (0.64)	10.75 (0.41)	11.04 (1.06)	0.89	0.45	11.09	0.00	0.40	0.53	1.38	0.25
	2	12.40 (0.59)	11.26 (0.59)	11.08 (0.38)	12.77 (0.98)								
Speed of	1	12.02 (0.63)	11.79 (0.60)	11.79 (0.40)	11.02 (1.02)	0.16	0.92	59.75	0.00	0.11	0.74	0.30	0.82
Comprehension	2	13.26 (0.63)	12.70 (0.60)	12.91 (0.41)	12.87 (1.02)								
Spot the word	1	9.95 (0.45)	10.43 (0.42)	9.85 (0.29)	9.51 (0.71)	0.81	0.49	95.46	0.00	0.001	0.98	0.61	0.61
	2	10.58 (0.43)	11.24 (0.40)	10.59 (0.28)	11.33 (0.68)								

#All significant group main effects, for the model with NART as a co-variate, were examined using least squares difference based on the marginal means.

¤ Group differences were investigated by means of the marginal means, 0≠3, 1≠3,

* Group differences were investigated by means of the marginal means, 0≠2, 1≠2,0=3 (trend p=0.06), 1=3 (trend, p=0.08)

Table 9.4. The results of the regression analyses of genetic liability and baseline neuropsychological assessment scores.

Variable	Significance of overall model		Regression coefficient for Genetic liability		Regression coefficient for NART		R^2
	F	P	t	P	t	P	
Full Scale IQ	0.24	0.63	-0.48	0.63			0.002
Verbal IQ	0.02	0.88	-0.15	0.88			0.00
Performance IQ	0.48	0.49	-0.69	0.49			0.003
NART	0.25	0.61	-0.50	0.61			0.005
NART-FSIQ difference	0.55	0.46	0.74	0.46			0.004
Total Hayling errors	1.59	0.21	1.51	0.13	-0.88	0.38	0.021
Hayling errors A	2.23	0.11	2.10	0.04	-0.11	0.91	0.03
Hayling errors B	0.74	0.48	0.54	0.59	-1.07	0.29	0.10
Block Design	19.37	0.00	-0.84	0.40	6.13	0.00	0.21
Block Design	1.46	0.23	-1.21	0.23			0.01
RBMT standardised score	7.94	0.001	-1.24	0.22	3.72	0.00	0.10
RBMT Story Immediate	10.46	0.00	-0.63	0.53	4.49	0.00	0.12
RBMT Story Delayed	12.95	0.00	-1.62	0.11	4.73	0.00	0.15
RAVLT trial I	2.86	0.06	1.63	0.10	1.85	0.07	0.04
RAVLT trials I-V	10.00	0.00	0.23	0.82	4.55	0.00	0.13
RAVLT delayed recall	6.75	0.002	-0.57	0.57	3.59	0.00	0.09
Factor_2	-3.24	0.001	-1.91	0.06	3.39	0.001	0.10
Factor_2 (NART not in model)	4.58	0.03	-2.14	0.03			0.03
Composite Memory score	2.54	0.11	-1.59	0.11			0.02
Digit symbol	12.41	0.00	0.92	0.36	4.93	0.00	0.14
Animals	7.75	0.001	-1.56	0.12	3.55	0.001	0.10

Table 9.5. The results of the regression analyses of genetic liability and the difference between time one and time two assessments.

Variable	Significance of overall model		Regression coefficient for Genetic liability		Regression coefficient for NART		R^2	Genetic Liability *	
	F	P	F	P	F	P		F	P
Total Hayling errors	0.99	0.38	1.31	0.19	0.41	0.68	0.03	1.69	0.20
Hayling errors A	2.71	0.07	2.14	0.04	0.72	0.47	0.07	2.99	0.09
Hayling errors B	0.06	0.94	0.35	0.73	-0.09	0.93	0.002	0.54	0.46
Block Design	0.16	0.85	-0.26	0.79	-0.48	0.64	0.005	0.33	0.57
RBMT standardised score	0.46	0.63	-0.95	0.34	-0.10	0.92	0.013	2.15	0.15
RBMT Story Immediate	4.11	0.02	-2.84	0.006	-0.21	0.83	0.10	0.11	0.74
RBMT Story Delayed	4.05	0.02	-2.84	0.006	0.32	0.75	0.10	0.53	0.47
RAVLT I	0.45	0.62	0.64	0.52	0.66	0.51	0.01	3.42	0.07
RAVLT I-V	0.43	0.65	-0.87	0.39	0.37	0.71	0.01	0.09	0.92
RAVLT delayed recall	1.23	0.30	-1.44	0.15	-0.54	0.59	0.01	0.00	0.99
Digit symbol	0.02	0.98	0.21	0.83	0.02	0.98	0.001	0.98	0.35
Animals	0.29	0.75	-0.07	0.94	0.77	0.45	0.01	1.40	0.24
Speed of comprehension	0.74	0.48	-1.17	0.25	-0.28	0.78	0.02	0.24	0.63
Spot the word	0.06	0.94	-0.16	0.88	-0.30	0.77	0.002	0.52	0.47

*Effect of genetic liability from a repeated measures analyses of variance with NART and Genetic liability as co-variates in the analyses (analyses based on ranks were appropriate)
The purpose of this was to estimate the effect of genetic liability on the original scores and not just on the differences as the differences don't tell us anything about the original scores.

9.4. Handedness variables in relation to family history within the high-risk group

9.4.1. Qualitative analysis

A chi-square analysis was conducted between the categorical handedness variables (described in detail in chapter 7) and the family history categories, at least two second degree relatives, one first and at least one second degree relative, and at least two first degree relatives. The categorical handedness variables included both the Annett and Oldfield scales categorised according to the Annett criteria for both demonstration 1 and verbal recall trials. Also the laterality quotients (LQs) for the Annett and Oldfield scales, for demonstration trial 1 and verbal recall were, recoded according to the 100%, 90%, and 80% cut-off criteria. No significant differences were found between the family history groups for any definition of handedness. However when family history was defined as having a parent with psychosis or not, the HR subjects who had a parent with a history of psychosis were significantly (chi-square=7.42, p=0.02) more likely to be mixed handed than those without such a family history. Mixed handedness, was defined by the first demonstration trial of the Annett scale according to the Annett classification system.

9.4.2. Family history and laterality quotients

Kruskal-Wallis one way ANOVA was conducted to assess the differences between family history groups and the quantitative LQs (generation of the LQs was described in detail in chapter 7). Again, no significant differences were observed between the categories. There was a significant positive correlation between the quantitative measure of genetic liability (described in chapter 9) and handedness (for demonstration trial one of the Annett scale) classified according to the Annett system (rho=0.24, p=0.009). This indicates that increasing genetic liability scores are associated with an increasing shift away from dextrality.

9.5. Family History for Schizophrenia according to symptomatology as measured on the PSE.

9.5.1.Statistical analyses

A description of the PSE is given in chapter 2 section 2.6.13. Non-parametric statistical analyses were conducted on the quantitative measure of genetic liability as it was not normally distributed. Mann-Whitney U tests for two groups and Kruskal-Wallis oneway analysis of variance for three or more groups. Symptoms according to the PSE at first visit, as outlined in chapter 2 Table 2.6.13.1, were dichotomised into whether psychotic symptoms were absent (study PSE scores of 0 or 1) or present (study PSE scores of 2,3, and 4) as outlined in section 2.6.13 of chapter 2. Also a cumulative dichotomised symptom variable was created, where subjects highest PSE scores ever (over the 3 assessments) were rated in the manner described above. Also an ordinal measure of PSE symptoms ever, (0-4) was analysed (chapter 2, Table 2.6.13.2.). For the categorical measure of family history, chi-square analyses were conducted with the dichotomised symptom variables and a Kruskal-Wallis oneway analysis of variance was conducted with family history (1,2, and 3) as categories and PSE scores as the dependent variable.

9.5.2 Results; symptoms and genetic liability

For the dichotomised variable, symptoms at first visit, there was no significant difference ($z=-0.78$, $p=0.44$) between those with symptoms absent (n=113, mean rank, 78.13) and those with symptoms present (n=39, mean rank 71.77) in terms of genetic liability. For the dichotomised variable, symptoms ever, there were no significant difference ($z=-0.63$, $p=0.53$) between those with symptoms absent (n=108, mean rank, 79.50) and those with symptoms present (n=47, mean rank 74.56) in terms of genetic liability. For the ordinal variable of symptoms ever (categories 0-4, chapter 2 Table), a Kruskal-Wallis oneway ANOVA revealed no significant differences between the symptom categories for genetic liability ($\chi^2=4.06$, df 4, $p=0.40$).

Chi-squared analysis comparing dichotomised symptoms at time of first visit revealed no significant differences ($\chi^2 = 2.62$, df 2, p=0.27) between the family history categories and symptom rate (analysis was confined to the high-risk group). Chi-squared analysis comparing dichotomised symptoms ever revealed no significant differences ($\chi^2 = 4.84$, df 2, p=0.09) between the family history categories and symptom rate (analysis was confined to the high-risk group). The results of the Kruskal-Wallis test comparing the ordinal highest PSE ratings ever obtained suggested no differences between the family history groups ($\chi^2 = 5.21$, df 2, p=0.07).

9.6.1 Relationship between social factors and maternal /parental family history within the high-risk group

As having a parent with schizophrenia is likely to have social implications it was decided to evaluate the socio-demographic variables according to whether the subject had a mother/parent with a schizophrenic illness or did not. For this analyses then, family history was dichotomised as having a mother/parent with schizophrenia or not. Logistic regression was employed as the method of statistical analyses.

9.6.2. Comparison of social variables for offspring of affected mothers versus those of unaffected mothers.

In Table 9.6 the socio-demographic variables are outlined comparing those in the high-risk group with an affected mother to those with other family histories. The variable, educational problems, was generated form the addition of five variables, including, qualifications, reading difficulties, speech problems, residential school attendance, and truancy, and was categorised as none, one or two, or three or more. The results of individual chi-squared analyses are presented in the Table. Those with an affected mother were found to have had significantly more social work involvement, and were in foster care significantly more often, than those without an affected mother. Also there was a trend (p=0.07) towards fewer forensic contacts in the offspring of affected mothers.

Backward logistic regression was conducted to see if the above variables could correctly predict if subjects had a mother with schizophrenia (the dichotomous

dependent variable). The model incorporated the following variables as independent variables; educational problems, psychological difficulties, forensic history, social work involvement, and in addition social class at origin was entered in order to control for its effect on the relationship between mother's illness and the above independent variables. A significant model was achieved (chi 26.27, df2, p=0.0000), with an overall sensitivity of 40% and a specificity of 93% (showing few false positives; i.e. rarely falsely identifying subjects as offspring of schizophrenic mothers who were not). The model indicated that two variables in particular were related to whether the mother had a diagnosis of schizophrenia or not. The variables retained in the model were forensic history (OR=0.46, p=0.005) and social work involvement (OR= 2.84, p<0.0001). Suggesting that offspring of mothers with schizophrenia were significantly less likely to have a forensic history compared to those with other family histories and that they were significantly more likely to have had social work involvement during their lives than those with other family histories. This model confirmed the findings of the individual analysis.

Table 9.6 Comparison of social variables for offspring of affected mothers versus those of unaffected mothers.

		Mother Affected n=43 n (%)	Other Affected n=112 n (%)	χ^2	P
Education problems	**0**	2 (4.9)	3 (2.7)		
	1-2	37 (90.2)	102 (91.1)	0.54	0.76
	3+	2 (4.9)	7 (6.3)		
Psychological difficulties	**No**	26 (60.5)	74 (66.1)		
	Yes	17 (39.5)	38 (33.9)	0.42	0.51
Social work involvement	**No**	20 (47.6)	91 (81.3)		
	Yes	22 (52.4)	21 (18.8)	17.16	**0.00003**
Forensic History	**No**	36 (83.7)	78 (69.6)		
	Yes	7 (16.3)	34 (30.4)	3.16	0.07
Foster care	**No**	33 (78.6)	106 (94.6)		
	Yes	9 (21.4)	6 (5.4)	8.97	**0.003**
Qualifications: Left before exams		6 (14.6)	8 (7.1)		
Leaving exam		35 (85.4)	105 (92.9)	2.08	0.15
Speech Problems	**No**	38 (90.5)	96 (85.7)		
	Yes	4 (9.5)	16 (14.3)	0.61	0.43
Reading difficulties	**No**	33 (78.6)	95 (84.8)		
	Yes	9 (21.4)	17 (15.2)	0.85	0.36
Truancy	**No**	35 (83.3)	95 (84.8)		
	Yes	7 (16.7)	17 (15.2)	0.51	0.82
Residential School	**No**	40 (95.2)	109 (97.3)		
	Yes	2 (4.8)	3 (2.7)	0.42	0.51

9.6.3. Comparison of social variables for offspring of affected parents versus those of unaffected parents within the high-risk group.

In Table 9.7 the socio-demographic variables are outlined comparing those in the high-risk group with an affected parent to those without an affected parent. The analysis conducted was identical to that in the previous section. Social work involvement and being in foster care (not independent variables) were found to have occurred significantly more often in the lives of those with an affected parent compared to those without.

Backward logistic regression was conducted to see if subjects with an affected parent (dependent variable) could be predicted. The model incorporated the following independent variables; education problems, psychological difficulties, forensic history, social work involvement, and in addition social class was entered in order to control for its effect on the relationship between parental illness and the above independent variables. A significant model was achieved (χ^2=24.90, df 4, p=0.0001), with an overall sensitivity of 46% and specificity of 84% (showing few false positives; i.e. rarely falsely identifying subjects as offspring of a schizophrenic parent when they were not). The model indicated that two variables in particular were related to whether the parent had a diagnosis of schizophrenia or not. The variables retained in the model and relating to parental illness were; being a member of social classes three or four (non manual/ skilled manual; OR=2.01, p=0.06) compared to the three other social class groups, and whether there was any social work involvement (OR=2.15, p=0.0002). This suggests that offspring of parents with schizophrenia in the current sample, are more likely to come from social class three or four and are significantly more likely to have had social work involvement during their lives than those with other family histories.

Table 9.7 Comparison of social variables for offspring of affected parents versus those of unaffected parents.

		Parent Affected n=65 n (%)	Other Affected n=91 n (%)	χ^2	P
Education problems	**0**	4 (6.3)	1 (1.1)		
	1-2	55 (87.5)	84 (93.3)	3.30	0.19
	3+	4 (6.3)	5 (5.6)		
Psychological difficulties	**No**	41 (63.1)	59 (65.6)		
	Yes	24 (36.9)	31 (34.4)	0.10	0.75
Social work involvement	**No**	35 (54.7)	76 (84.4)		
	Yes	29 (45.3)	14 (15.6)	16.46	**0.00005**
Forensic History	**No**	49 (75.4)	65 (72.2)		
	Yes	16 (26.6)	25 (27.8)	0.19	0.66
Foster care	**No**	53 (82.8)	86 (95.6)		
	Yes	11 (17.2)	4 (4.4)	6.91	**0.008**
Qualifications: Left before exams		9 (14.3)	5 (5.5)		
Leaving exam		54 (85.7)	86 (94.5)	3.48	0.06
Speech Problems	**No**	54 (84.4)	80 (88.9)		
	Yes	10 (15.6)	10 (11.1)	0.67	0.41
Reading difficulties	**No**	51 (79.7)	77 (85.6)		
	Yes	13 (20.3)	13 (14.4)	0.92	0.34
Truancy	**No**	51 (79.7)	79 (87.8)		
	Yes	13 (20.3)	11 (12.2)	1.86	0.17
Residential School	**No**	60 (93.8)	89 (98.9)		
	Yes	4 (6.3)	1 (1.1)	3.14	0.08

9.7. Discussion

The purpose of this Chapter was to examine the nature of the relationship, if any, between the degree of genetic liability for schizophrenia, and neuropsychological performance. In order to examine this relationship, the variables that distinguished the HR group from the controls at baseline were analysed according to family history of schizophrenia, using both a qualitative and a quantitative method of describing family history.

Family history for schizophrenia was related to measures of handedness, and to the presence of psychotic symptoms. Finally the socio-demographic variables were examined according to family history for schizophrenia using logistic regression analysis.

Increased HSCT errors A (correct completion of the sentence, when an incorrect response is required) and reduced factor scores for Factor 2 (factor loading on performance IQ/ visuo-spatial performance), distinguished different categories of family history within the HR group. Using the quantitative measure (which was only calculated for the HR group) this result was confirmed and a significant effect of genetic liability was seen in the regression analyses for these variables. At follow-up there appeared to be a genetic dosage effect for the standardised RBMT scores, with higher degrees of genetic loading associated with lower scores. The CPT-IP measures were not related to measures of genetic liability.

In summary the results suggested that aspects of executive function, memory and visuo-spatial ability are associated with degree of familial risk, and familial risk appeared to be associated with degree of change in performance over time.

There are many reasons why deficits in performance might be related to the degree of familial risk. Apart from any genetic explanation, living in the same environment as a person with schizophrenia may be detrimental to development. It is likely more detrimental if the affected family member is a parent who has been ill through all or

a substantial part of the offspring's development rather than if it is a sibling who has recently developed the illness. In this sample we did not define our groups in this manner. The two groups with first degree relatives affected (Fhx2 and Fhx3) were similar in terms of who was affected. For Fhx2 (one first degree relative affected) 43% had a mother affected, 21% a father, and 36% a sibling, for Fhx3 (more than one first degree relative affected) 45% had a mother, 25% a father, and 30% had 2 siblings affected.

There were no subjects who had both a mother and a father affected. However having a mother or parent was associated with more social work involvement, with social class 3 or 4 and with reduced forensic contacts. It was not associated with an increase in educational difficulties which suggests that the difficulty are not just due to social deprivation or underachievement due to parental illness. Also, 30% had 2 affected siblings and no affected parents, so the explanation for increased deficits in those at highest risk is unlikely to be a social one, but this cannot be ruled out at this time. To our knowledge other studies have not examined the results in this manner. It is interesting that aspects of neuropsychological functioning that consistently appear to be impaired in the HR and patient groups compared to controls, namely aspects of the HSCT, memory, and visuo-spatial ability, are also associated with degree of genetic risk within the HR group.

Interestingly the presence of psychotic symptoms was not related to the measures of genetic liability with the HR group. The increased genetic liability was associated with handedness and specifically with a shift away from dextrality. An increase in non-right handedness, in both patients with schizophrenia (Satz and Green, 1999), and in the relatives of such patients (Orr et al., 1999) has been previously reported. It has been outlined in detailed in Chapter 7. Crow (1997) and Annett (1999) interpreted the shift from dextrality as indicating that schizophrenia may be due to a genetically caused anomaly of cerebral dominance. Yeo (1999) suggested that this relationship might best be understood as a result of developmental instability causing a veering away from the expected course of development.

Developmental instability is often quantified as a measure of fluctuating asymmetry (FA; random differences between left and right sides), particularly in dermatoglyphic features (fingerprints) and dental structures. Waddington (1957) developed the concept of canalisation, the basic premise of which was that genetic factors channel development along adaptive pathways, and any changes from this developmental pathway, was believed to be under genetic control. Increased instability as measured by FA, might be seen in a deviated developmental pathway that normally is buffered, and this could be due to an environmental insult or to a deficit in the genome (Rose et al., 1987). Under this theory a single adverse intrauterine event may be completely buffered and inconsequential in one organism while being detrimental to another. Buffering ability has been found to be dependent upon levels of heterozygosity across the entire genotype, with greater numbers of heterozygous loci being associated with increased developmental stability and bilateral symmetry (Markow and Gottesman, 1989b). FA has been interpreted to be under polygenic control and has been found in patients with schizophrenia (Markow and Wander, 1986; Markow and Gottesman, 1989a, 1989b; Mellor 1992). While regarding genetics as necessary, a role for the environment is allowed. Markow and Gottesman (1989b) studied twins with schizophrenia and concluded that as discordant twins show less FA that they may have a lower 'gene dosage' than concordant twins. An increase in FA was seen in the offspring of monkeys who were stressed during pregnancy (Newell-Morris et al., 1989). In this study, dermatoglyphic data and measures of minor physical anomalies (MPA's) have been collected so it will be possible to investigate FA at a future date.

The implications are that developmental instability can lead to deviant pathways of development, these can be measured as deviations from the normal patterns of symmetry or asymmetry in anatomical structures and may be caused by genetic and /or environmental factors. This model suggests that many different and inconsistent patterns of deviance could be identified and this may help to explain the great diversity of findings across all kinds of studies in schizophrenia, including brain imaging studies.

The deficits seen in the high-risk group compared to controls on tasks of executive function, memory, and visuo-spatial ability may be a product of such a deviant mechanism, which caused aberrant development of the relevant brain systems, and may have greater effect in those with higher genetic loadings, who may have more compromised buffering abilities. A major problem is the lack of knowledge about the true mode of genetic transmission.

Overall it would appear that what is inherited is the vulnerability to schizophrenia and not the disorder itself. This vulnerability is manifested by fairly widespread neuropsychological impairments, particularly in areas of memory and executive functioning, and by a shift from dextrality, which are nonetheless, compatible with competent functioning.

Chapter Ten: Summary and Conclusions

The aim of this thesis was to present the neuropsychological assessment results from the Edinburgh High Risk for Schizophrenia Study within the context of the study as a whole. Given the nature of this study, and with regard to the development of symptoms the story is a changing one and it will not be possible to give a definite answer about the true nature of the relationship between neuropsychological functioning in the high-risk group and the development of schizophrenia until all the members of the group have passed through the risk period. However, at this stage it was deemed important to outline the baseline and follow-up results and to present the current state of our knowledge regarding neuropsychological functioning in the high-risk sample.

This study required a large amount of energy and effort from everyone involved especially the subjects who gave up their free time, often repeatedly, to help us with our research. This sample can be thought of as a national resource, which will help elucidate the factors that predate psychosis in the high-risk group. In comparison to the other so called first generation high-risk studies, it is unique in that subjects were recruited in early adulthood, thus limiting the degree of attrition and avoiding the problem of non-comparability of age related test effects and dating of instruments used in the assessments. The study is also strengthened by the current availability of sophisticated scanning technology, both structural and functional, which it is hoped, will help to achieve the ultimate goal of plotting the course to onset and the precursors of illness in this group. Other studies of the same aim have used a different definition of risk (see Cornblatt and Obuchowski, 1997), defining risk for schizophrenia on the basis of a behavioural change and not on a genetic basis. This type of research presents a tremendous problem in that those defined as at risk due to behavioural changes in early adulthood may have already crossed an important threshold or may never develop schizophrenia. It is difficult to randomly identify those at risk according to these criteria, as one of the only identified risk factors is a family predisposition.

It might appear that the first generation high risk studies have not been very successful in elucidating the precursors and risks for schizophrenia in those

genetically identified subjects, however it is for many of the reasons stated above, such as high rates of attrition and the long time delay between recruitment and the development of illness that the high risk studies have not realised their full potential (Erlenmeyer-Kimling and Cornblatt, 1987).

The sample reported upon here, included only 162 of the 229 identified subjects, and the 229 identified individuals who consented to take part do not likely represent the total number of high-risk subjects in Scotland for many reasons. Because of the ethical considerations involved in recruiting the sample, all contacts had to first go through the index patient and in some cases such patients did not consent for us to contact the family. Sometimes, the subject had moved abroad and was not available to participate. In addition it is likely that some individuals were adopted at birth. In the absence of a national tracking for example like that available in the Scandinavian countries, the identification of a total epidemiological sample of all high-risk subjects in Scotland was not possible. However all the subjects who took part in the project were well at entry, had a genetic predisposition by virtue of their family history, and had a similar socio-demographic profile to the control group which would indicate that they are representative, at least of the general population in Scotland. In time the relevance of the control group will diminish as the high-risk group will become their own controls and it will be possible to compare those who remain well with those who developed the illness, however at this point in time, comparison to the control group is essential.

The neuropsychological test results are only one aspect of this study, an extensive library of data has been collected concerning obstetric complications, dermatoglyphics, minor physical anomalies, neurological soft signs, brain imaging data, information relating to childhood behaviour, clinical interviews, and information regarding life events. This study therefore, has great potential to shed light on the mechanisms through which an individual develops schizophrenia, and to elucidate risk factors for the development of schizophrenia and any interactions between the factors and genetic risk.

A large volume of data was presented. A large number of uncorrected univariate analyses were conducted in addition to the multivariate approaches. The justification for this way of dealing with the data is that given the valuable nature of the sample and the broad areas investigated, fine investigation was warranted and it was felt that all possible clues should be sought, at least at this stage. Any identifiable, even possible deficits could therefore be followed up and explored in greater detail and in time their meaning will no doubt become clearer.

At baseline assessment the high-risk group and the patients had lower IQ estimates than the control group, controlling for NART IQ deficits in the high risk group were observed in the areas of learning and memory, executive functioning and there was some evidence for deficits in visuo-spatial functioning. There were no differences between the high-risk group and the control group in terms of CPT-IP measures, but the patients were poorer at this task than the other groups. The findings from this study broadly confirm those of other studies of this nature, high-risk studies and studies of adult relatives of patients with schizophrenia. From the follow-up analyses presented in chapter six, the baseline findings were confirmed, and the presence of deficits in the areas of executive functioning and learning and memory were confirmed. In terms of lateral preferences, displayed in chapter seven, no group differences were identified, however, it did appear that patients responses became somewhat more consistent over time, perhaps suggesting unreliable reporting. There was evidence for a relationship between reduced dextrality and social and educational difficulties, particularly in the patient group.

The presence of symptoms did have an effect on neuropsychological performance, particularly on the areas of mental control encoding, perceptual motor speed, and learning and memory. Executive function did not appear to be affected by symptoms, however. An association between the presence of psychotic symptoms and reduced performance on the CPT-IP was evident. A new and important finding was that in those who developed symptoms between round one and round two, the processes of intellectual decline had begun prior to the onset of symptoms. In the high-risk group psychotic symptoms were related to indicators of disturbed

upbringing. A negative relationship was observed between family history and dextrality. In addition, aspects of executive functioning, memory, and visuo-spatial ability were associated with family history. Psychotic symptoms were not related to the degree of genetic risk within the high-risk group.

The findings of the present study indicate that what is inherited by individuals at enhanced risk for schizophrenia because of genetic liability is not the disorder itself, but a state of vulnerability manifested by fairly widespread neuropsychological impairments and by a shift from dextrality which are nevertheless compatible with competent functioning. Relationships between these impairments and the development of psychotic symptoms were demonstrated, but were relatively few and the genetically acquired state of vulnerability must frequently exist without the development of psychotic symptomatology. The development of symptoms is a changing situation and at this stage definite conclusions cannot be made until the subjects have passed through the risk period. It appears that the presence of the genetically acquired state of vulnerability is not sufficient for the development of schizophrenia and some other factor or factors is required even when genetic predisposition is present.

At the present time it can be stated that those vulnerable to schizophrenia for genetic reasons have widespread cognitive impairment, which is evident before there is any evidence of psychotic features and are probably also present in those who will not develop the illness. Cognitive deterioration was evident in those who developed psychotic symptoms. The primary change may therefore be a deterioration of already impaired neuropsychological functioning. This is a new finding and has implications for the understanding of the schizophrenic process and for the consideration of strategies of early intervention.

It is believed that the full potential of the Edinburgh High Risk for Schizophrenia Study will be realised in time and it is hoped that this study will add significantly to the current state of our knowledge on the causes of schizophrenia.

Bibliography

Achenbach, T.M. (1993). Manual for the Child Behavior Checklist/ 4-18 and 1991 Profile. Burlington: University of Vermont.

Adams, W., Kendell, R.E., Hare, E.H., & Munk-Jorgensen, P. (1993). Epidemiological evidence that maternal influenza contributes to the aetiology of schizophrenia. An analysis of Scottish, English, and Danish data. Br J Psychiatry, 163, 522-534.

Akabaliev, V., & Sivkov, S. (1998). Minor physical anomalies in schizophrenia. Folia Med (Plovdiv), 40(2), 39-45.

Akbarian, S., Bunney, W.E.J., Potkin, S.G., Wigal, S.B., Hagman, J.O., Sandman, C.A., & Jones, E.G. (1993). Altered distribution of nicotinamide-adenine dinucleotide phosphate- diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Arch Gen Psychiatry, 50(3), 169-177.

Alanen, Y.O. (1958). The mothers of schizophrenic patients. Acta Psychiatr Scand, 33(Suppl 124), 1-361.

Aleman, A., Hijman, R., de Haan, E.H., & Kahn, R.S. (1999). Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry, 156(9), 1358-1366.

Allen, H.A., Liddle, P.F., & Frith, C.D. (1993). Negative features, retrieval processes and verbal fluency in schizophrenia [see comments]. Br J Psychiatry, 163, 769-775.

Altman, D.G. (1991). Practical Statistics for Medical Research. London: Chapman and Hall.

American Psychiatric Association. (1980). Diagnostic and Statistical Manual of Mental Disorders (3rd edition). Washington, DC: The Association.

American Psychiatric Association. (1987). Diagnostic and Statistical Manual of Mental Disorders (3rd edition, revised). Washington, DC: The Association.

American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders (4th edition). (4th ed.). Washington, DC: The Association.

Anastasi, A. (1988). Psychological Testing. (6th ed.). New York: MacMillan.

Andreasen, N., Nasrallah, H.A., Dunn, V., Olson, S.C., Grove, W.M., Ehrhardt, J.C., Coffman, J.A., & Crossett, J.H. (1986). Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. Arch Gen Psychiatry, 43(2), 136-144.

Andreasen, N.C., & Olsen, S. (1982). Negative v positive schizophrenia. Definition and validation. Arch Gen Psychiatry, 39(7), 789-794.

Andreasen, N.C., Dennert, J.W., Olsen, S.A., & Damasio, A.R. (1982). Hemispheric asymmetries and schizophrenia. Am J Psychiatry, 139(4), 427-430.

Andreasen, N.C., Shore, D., Burke, J.D.J., Grove, W.M., Lieberman, J.A., Oltmanns, T.F., Pettegrew, J.W., Pulver, A.E., Siever, L.J., & Tsuang, M.T. (1988). Clinical phenomenology. Schizophr Bull, 14(3), 345-363.

Andreasen, N.C., Ehrhardt, J.C., Swayze, V.W., Alliger, R.J., Yuh, W.T., Cohen, G., & Ziebell, S. (1990). Magnetic resonance imaging of the brain in schizophrenia. The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry, 47(1), 35-44.

Annett, M. (1970). A classification of hand preference by association analysis. Br J Psychol, 61(3), 303-321.

Annett, M. (1972). The distribution of manual asymmetry. Br J Psychol, 63(3), 343-358.

Annett, M. (1973). Handedness in families. Ann Hum Genet, 37(1), 93-105.

Annett, M. (1975). Hand preference and the laterality of cerebral speech. Cortex, 11(4), 305-328.

Annett, M. (1978). Genetic and nongenetic influences on handedness. Behav Genet, 8(3), 227-249.

Annett, M., & Ockwell, A. (1980). Birth order, birth stress and handedness. Cortex, 16(1), 181-187.

Annett, M. (1985). A gene for the right hand. New Scientist, (24th July), 20

Annett, M. (1985). Left, Right, Hand and Brain: The Right Shift Theory. London: Lawrence Erlbaum Associates Ltd.

Annett, M. (1991). Laterality and cerebral dominance. J Child Psychol Psychiatry, 32(2), 219-232.

Annett, M. (1992). Spatial ability in subgroups of left- and right-handers. Br J Psychol, 83 (Pt 4), 493-515.

Annett, M. (1999). The theory of an agnosic right shift gene in schizophrenia and autism. Schizophr Res, 39(3), 177-182.

Armitage, P. & Berry, G. (1994). Statistical Methods in Medical Research. (3rd ed.) Oxford: Blackwell.

Ardila, A., & Rosselli, M. (1989). Neuropsychological characteristics of normal aging. Developmental Neuropsychology, 5, 307-320.

Arnold, S.E., Hyman, B.T., Van Hoesen, G.W., & Damasio, A.R. (1991). Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. Arch Gen Psychiatry, 48(7), 625-632.

Asarnow, J.R., Steffy, R.A., & MacCrimmon, D.J. (1978). An Attentional Assessment of Foster Children at Risk for Schizophrenia. In Anonymous, The Nature of Schizophrenia: New Approaches to Research and Treatment. (pp. 339-358). New York: Wiley and Sons.

Asarnow, J.R. (1988). Children at risk for schizophrenia: converging lines of evidence. Schizophr Bull, 14(4), 613-631.

Asarnow, J.R., & Goldstein, M.J. (1986). Schizophrenia during adolescence and early adulthood: A developmental perspective on risk research. Clinical Psychology Review, 6(3), 211-235.

Asarnow, R.F., Steffy, R.A., MacCrimmon, D.J., & Cleghorn, J.M. (1977). An attentional assessment of foster children at risk for schizophrenia. J Abnorm Psychol, 86(3), 267-275.

Aylward, E., Walker, E., & Bettes, B. (1984). Intelligence in schizophrenia: meta-analysis of the research. Schizophr Bull, 10(3), 430-459.

Baddeley, A., Emslie, H., & Smith, I.N. (1992). The Speed and Capacity of Language-Processing Test. Bury St.Edmunds: Thames Valley Test Company.

Baddeley, A. (1992). Working memory. Science, 255(5044), 556-559.

Baddeley, A., Emslie, H., & Nimmo-Smith, I. (1993). The Spot-the-Word test: a robust estimate of verbal intelligence based on lexical decision. Br J Clin Psychol, 32 (Pt 1), 55-65.

Baddeley, A.D. (1986). Working Memory . Oxford: Clarendon.

Bakan, P. (1971). Handedness and birth order. Nature, 229(5281), 195

Bakan, P., Dibb, G., & Reed, P. (1973). Handedness and birth stress. Neuropsychologia, 11, 363-366.

Bakan, P. (1977). Left handedness and birth order revisited. Neuropsychologia, 15(6), 837-839.

Bakan, P. (1978). Handedness and birth order: a critical note on a critical note. Percept Mot Skills, 46(2), 556

Bakan, P. (1991). Handedness and maternal smoking during pregnancy. Int J Neurosci, 56(1-4), 161-168.

Barnes, F. (1975). Temperament, adaptability and left handedness. New Scientist, (67), 202-203.

Baron, M. (1986). Genetics of schizophrenia: II. Vulnerability traits and gene markers. Biol Psychiatry, 21(12), 1189-1211.

Barr, C.E., Mednick, S.A., & Munk-Jorgensen, P. (1990). Exposure to influenza epidemics during gestation and adult schizophrenia. A 40-year study. Arch Gen Psychiatry, 47(9), 869-874.

Bateson, G., Jackson, D.D.H.J., & Weakland, J.H. (1956). Toward a theory of schizophrenia behaviour. Behavioural Science, I, 251-264.

Beaton, A.L. (1985). Left Side, Right Side. New Haven, Conneticut: Yale University Press.

Benes, F.M., McSparren, J., Bird, E.D., SanGiovanni, J.P., & Vincent, S.L. (1991). Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. Arch Gen Psychiatry, 48(11), 996-1001.

Benton, A.L., Hamsher, K.d., Varney, N.R., & Spreen, O. (1983). Contributions to Neuropsychological Assessment. New York: Oxford University Press.

Benton, A.L. (1984). Constructional apraxia: an update. Seminars in Neurology, 4, 220-222.

Bilder, R.M., Lipschutz-Broch, L., Reiter, G., Geisler, S.H., Mayerhoff, D.I., & Lieberman, J.A. (1992). Intellectual deficits in first-episode schizophrenia: evidence for progressive deterioration. Schizophr Bull, 18(3), 437-448.

Bishop, D.V. (1990). How to increase your chances of obtaining a significant association between handedness and disorder. J Clin Exp Neuropsychol, 12(5), 812-816.

Bishop, D.V.M. (1983). How sinister is sinistrality? Journal of the Royal College of Physicians of London, 17, 161-172.

Bleuler, M. (1978). The Schizophrenic Disorders: Long-Term Patients and Family Studies (Translated by S. Clemens). New Haven: Yale University Press.

Bogerts, B., Meertz, E., & Schonfeldt-Bausch, R. (1985). Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. Arch Gen Psychiatry, 42(8), 784-791.

Bogerts, B., Ashtari, M., Degreef, G., Alvir, J.M., Bilder, R.M., & Lieberman, J.A. (1990). Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res, 35(1), 1-13.

Bolla-Wilson, K., & Bleecker, M.L. (1986). Influence of verbal intelligence, sex, age, and education on the Rey Auditory Verbal Learning Test. Developmental Neuropsychology, 2(3), 203-211.

Book, J.A. (1953). A genetic and neuropsychiatric investigation of a North Swedish population (with special regard to schizophrenia and mental deficiency). Acta Genetica, 4, 1-1000.

Book, J.A., Wetterberg, L., & Modrzewska, K. (1978). Schizophrenia in a north Swedish geographical isolate 1900-1977: epidemiology, genetics and biochemistry. Clin Genet, 14, 373-394.

Bracha, H.S., Torrey, E.F., Bigelow, L.B., Lohr, J.B., & Linington, B.B. (1991). Subtle signs of prenatal maldevelopment of the hand ectoderm in schizophrenia: a preliminary monozygotic twin study. Biol Psychiatry, 30(7), 719-725.

Bracha, H.S. (1991). Etiology of structural asymmetry in schizophrenia: an alternative hypothesis [letter]. Schizophr Bull, 17(4), 551-553.

Bracha, H.S., Torrey, E.F., Gottesman, I.I., Bigelow, L.B., & Cunniff, C. (1992). Second-trimester markers of fetal size in schizophrenia: a study of monozygotic twins [see comments]. Am J Psychiatry, 149(10), 1355-1361.

Brocha, P. (1861). Remarques sur la siege de la faculte du langue. Bulletin de la Societe Anatomique de Paris (2nd series), 6, 330-357.

Bromet, E.J., & Fennig, S. (1999). Epidemiology and natural history of schizophrenia [see comments]. Biol Psychiatry, 46(7), 871-881.

Brown, G.W., Birley, J.L., & Wing, J.K. (1972). Influence of family life on the course of schizophrenic disorders: a replication. Br J Psychiatry, 121(562), 241-258.

Bruton, C.J., Crow, T.J., Frith, C.D., Johnstone, E.C., Owens, D.G., & Roberts, G.W. (1990). Schizophrenia and the brain: a prospective clinico-neuropathological study. Psychol Med, 20(2), 285-304.

Bryden, M.P. (1977). Measuring handedness with questionnaires. Neuropsychologia, 15(4-5), 617-624.

Bryden, M.P. (1982). Laterality: Functional Asymmetry in the Intact Brain. New York: Academic Press.

Buchanan, R.W., & Heinrichs, D.W. (1989). The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res, 27(3), 335-350.

Buchanan, R.W., Strauss, M.E., Kirkpatrick, B., Holstein, C., Breier, A., & Carpenter, W.T.J. (1994). Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. Arch Gen Psychiatry, 51(10), 804-811.

Buchsbaum, M.S., Nuechterlein, K.H., Haier, R.J., Wu, J., Sicotte, N., Hazlett, E., Asarnow, R., Potkin, S., & Guich, S. (1990). Glucose metabolic rate in normals and schizophrenics during the Continuous Performance Test assessed by positron emission tomography. Br J Psychiatry, 156, 216-227.

Burgess, A., Flint, J., & Adshead, H. (1992). Factor structure of the Wechsler Adult Intelligence Scale--Revised (WAIS--R): A clinical sample. British Journal of Clinical Psychology, 31(3), 336-338.

Burgess, P.W., & Shallice, T. (1996). Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia, 34(4), 263-272.

Burton, D.B., Ryan, J.J., Paolo, A.M., & Mittenberg, W. (1994). Structural equation analysis of the Wechsler Adult Intelligence Scale--Revised in a normal elderly sample. Psychological Assessment, 6(4), 380-385.

Byrne, M., Hodges, A., Grant, E., Owens, D.C., & Johnstone, E.C. (1999). Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS). Psychol Med, 29(5), 1161-1173.

Byrne, M., Browne, R., Mulryan, N., Scully, A., Morris, M., Kinsella, A., Takei, N., McNeil, T.F., Walsh, D., & O'Callaghan, E. (2000). Labour and delivery complications and schizophrenia. British Journal of Psychiatry, 176(May)

Campbell, M., Geller, B., Small, A.M., Petti, T.A., & Ferris, S.H. (1978). Minor physical anomalies in young psychotic children. Am J Psychiatry, 135(5), 573-575.

Cannon, M., Byrne, M., Cassidy, B., Sheppard, N., Larkin, C., & O'Callaghan, E. (1993). Dermatoglyphic fluctuating asymmetry and handedness in schizophrenia. Schizophr Res, 9, 172

Cannon, M., Byrne, M., Cassidy, B., Larkin, C., Horgan, R., Sheppard, N.P., & O'Callaghan, E. (1995). Prevalence and correlates of mixed-handedness in schizophrenia. Psychiatry Res, 59(1-2), 119-125.

Cannon, M., Cotter, D., Coffey, V.P., Sham, P.C., Takei, N., Larkin, C., Murray, R.M., & O'Callaghan, E. (1996). Prenatal exposure to the 1957 influenza epidemic and adult schizophrenia: a follow-up study [see comments]. Br J Psychiatry, 168(3), 368-371.

Cannon, M., Jones, P., Murray, R.M., & Wadsworth, M.E. (1997). Childhood laterality and later risk of schizophrenia in the 1946 British birth cohort. Schizophr Res, 26(2-3), 117-120.

Cannon, T.D., Mednick, S.A., Parnas, J., Schulsinger, F., Praestholm, J., & Vestergaard, A. (1993). Developmental brain abnormalities in the offspring of schizophrenic mothers. I. Contributions of genetic and perinatal factors [see comments]. Arch Gen Psychiatry, 50(7), 551-564.

Cannon, T.D., & Mednick, S.A. (1993). The schizophrenia high-risk project in Copenhagen: three decades of progress. Acta Psychiatr Scand Suppl, 370, 33-47.

Cannon, T.D., Mednick, S.A., Parnas, J., Schulsinger, F., Praestholm, J., & Vestergaard, A. (1994). Developmental brain abnormalities in the offspring of schizophrenic mothers. II. Structural brain characteristics of schizophrenia and schizotypal personality disorder. Arch Gen Psychiatry, 51(12), 955-962.

Cannon, T.D., Rosso, I.M., Bearden, C.E., Sanchez, L.E., & Hadley, T. (1999). A prospective cohort study of neurodevelopmental processes in the genesis and epigenesis of schizophrenia. Dev Psychopathol, 11(3), 467-485.

Carlsson, A., & Lindqvist, M. (1963). Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacological et Toxicologica, 20, 140-144.

Carlsson, A. (1987). Historical Perspective of the Chemistry and Pharmacologyical Treatment of Schizophrenia. In F. A. Henn & L. E. DeLisi (Eds.), Handbook of Schizophrenia. Volume 2: Neurochemistry and Neuropharmacology of Schizophrenia. (pp. 1-17). Amsterdam: Elsevier Scientific Publishers.

Carter-Saltzman, L. (1980). Biological and sociocultural effects on handedness: comparison between biological and adoptive families. Science, 209(4462), 1263-1265.

Censits, D.M., Ragland, J.D., Gur, R.C., & Gur, R.E. (1997). Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. Schizophr Res, 24(3), 289-298.

Chaguale, V.B., & Masters R.S. (1981). Impaired cerebral dominance and schizophrenia. British Journal of Psychiatry, 139, 23-24.

Chapman, J.P., & Chapman, L.J. (1987). Handedness of hypothetically psychosis-prone subjects. J Abnorm Psychol, 96(2), 89-93.

Chapman, L.J., & Chapman, J.P. (1978). The measurement of differential deficit. J Psychiatr Res, 14(1-4), 303-311.

Chapman, L.J., & Chapman, J.P. (1989). Strategies for resolving the heterogeneity of schizophrenics and their relatives using cognitive measures. J Abnorm Psychol, 98(4), 357-366.

Chase, T.N., Fedio, P., Foster, N.L., Brooks, R., Di Chiro, G., & Mansi, L. (1984). Wechsler Adult Intelligence Scale performance. Cortical localization by

fluorodeoxyglucose F 18-positron emission tomography. Arch Neurol, 41(12), 1244-1247.

Chen, E.Y., Lam, L.C., Chen, R.Y., Nguyen, D.G., & Chan, C.K. (1996). Prefrontal neuropsychological impairment and illness duration in schizophrenia: a study of 204 patients in Hong Kong. Acta Psychiatr Scand, 93(2), 144-150.

Chodirker, B.N., Chudley, A.E., Ray, M., Wickstrom, D.E., & Riordan, D.L. (1987). Fragile 19p13 in a family with mental illness. Clin Genet, 31(1), 1-6.

Chua, S.E., & McKenna, P.J. (1995). Schizophrenia--a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. Br J Psychiatry, 166(5), 563-582.

Churchill, J.A. (1962). The association of position at birth and handedness. Pediatrics, 29, 307-309.

Clare, L., McKenna, P.J., Mortimer, A.M., & Baddeley, A.D. (1993). Memory in schizophrenia: what is impaired and what is preserved? Neuropsychologia, 31(11), 1225-1241.

Clementz, B.A., Iacono, W.G., & Beiser, M. (1994). Handedness in first-episode psychotic patients and their first-degree biological relatives. J Abnorm Psychol, 103(2), 400-403.

Cloninger, C.R. (1994). Turning point in the design of linkage studies of schizophrenia. Am J Med Genet, 54(2), 83-92.

Clyma, E.A. (1972). Hand and eye dominance in schizophrenia. Br J Psychiatry, 121(564), 576

Coffey, V.P., & Jessop, W.J. (1959). Maternal influenza and congenital deformities: a prospective study. Lancet, ii , 935-938.

Cohler, B.J., Grunebaum, H.U., Weiss, J.L., Gamer, E., & Gallant, D.H. (1977). Disturbance of attention among schizophrenic, depressed and well mothers and their young children. J Child Psychol Psychiatry, 18(2), 115-135.

Condray, R., Steinhauer, S.R., & Goldstein, G. (1992). Language comprehension in schizophrenics and their brothers. Biol Psychiatry, 32(9), 790-802.

Condray, R., & Steinhauer, S.R. (1992). Schizotypal personality disorder in individuals with and without schizophrenic relatives: similarities and contrasts in neurocognitive and clinical functioning. Schizophr Res, 7(1), 33-41.

Conklin, H.M., Curtis, C.E., Katsanis, J., & Iacono, W.G. (2000). Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. Am J Psychiatry, 157(2), 275-277.

Connor, A., Franzen, M.D., & Sharp, B. (1988). Effects of practice and differential instructions on Stroop performance. International Journal of Clinical Neuropsychology, 10(1), 1-4.

Conover, W.J., & Iman, R.L. (1982). Analysis of covariance using the rank transformation. Biometrics, 38(3), 715-724.

Conrad, A.J., Abebe, T., Austin, R., Forsythe, S., & Scheibel, A.B. (1991). Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon. Arch Gen Psychiatry, 48(5), 413-417.

Cooper, J.E., Kendell R.E., Gurland, B.J., Sharpe, L., Copeland, J.R.M., & Simon, R. (1972). Psychiatric Diagnosis in New York and London: a Comparative Study of Mental Hospital Admissions. London: Oxford University Press.

Corballis, M.C., & Morgan, M.S. (1978). On the biological basis of human laterality: 1. Evidence for a maturational left-right gradient. Behavioural Brain Science, 2, 261-336.

Corballis, M.C. (1983). Human Laterality. Orlando, Florida: Academic Press Inc.

Coren, S., & Porac, C. (1979). Normative data on hand position during writing. Cortex, 15(4), 679-682.

Coren, S., Porac, C., & Duncan, P. (1981). Lateral preferences behaviours in preschool children and young adults. Child Dev, 52, 443-450.

Coren, S., & Halpern, D.F. (1991). Left-handedness: a marker for decreased survival fitness [see comments]. Psychol Bull, 109(1), 90-106.

Coren, S., Searleman, A., & Porac, C. (1986). Rate of physical maturation and handedness. Developmental Neuropsychology, 2(1), 17-23.

Cornblatt, B., Obuchowski, M., Schnur, D.B., & O'Brien, J.D. (1997). Attention and clinical symptoms in schizophrenia. Psychiatr Q, 68(4), 343-359.

Cornblatt, B.A., & Erlenmeyer-Kimling, L. (1985). Global attentional deviance as a marker of risk for schizophrenia: specificity and predictive validity. J Abnorm Psychol, 94(4), 470-486.

Cornblatt, B.A., Risch, N.J., Faris, G., Friedman, D., & Erlenmeyer-Kimling, L. (1988). The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiatry Res, 26(2), 223-238.

Cornblatt, B.A., Lenzenweger, M.F., Dworkin, R.H., & Erlenmeyer-Kimling, L. (1992). Childhood attentional dysfunctions predict social deficits in unaffected adults at risk for schizophrenia. Br J Psychiatry Suppl, (18), 59-64.

Cornblatt, B.A., & Keilp, J.G. (1994). Impaired attention, genetics, and the pathophysiology of schizophrenia [published erratum appears in Schizophr Bull 1994;20(2):248]. Schizophr Bull, 20(1), 31-46.

Cornblatt, B., & Erlenmeyer-Kimling, L. (1984). Early attentional predictors of adolescent behavioral disturbances in children at risk for schizophrenia. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 198-211). Cambridge, England UK: Cambridge University Press.

Cornblatt, B., Winters, L., & Erlenmeyer-Kimling, L. (1989). Attentional markers of schizophrenia: Evidence from the New York High-Risk Study. In S. C. Schulz, C. A. Tamminga, & a. et (Eds.), Schizophrenia: Scientific progress. (pp. 83-92). New York, NY, USA: Oxford University Press.

Cornblatt, B., & Obuchowski, M. (1997). Update of high-risk research: 1987-1997. International Review of Psychiatry, 9, 437-447.

Cornblatt, B.A., Dworkin, R.H., Wolf, L.E., & Erlenmeyer-Kimling, L. (1996). Markers, developmental processes, and schizophrenia. In M. F. Lenzenweger, J. J. Haugaard, & a. et (Eds.), Frontiers of developmental psychopathology. (pp. 125-147). New York, NY, USA: Oxford University Press.

Crawford, J.R., Stewart, L.E., Garthwaite, P.H., Parker, D.M., & Besson, J.A. (1988). The relationship between demographic variables and NART performance in normal subjects. Br J Clin Psychol, 27 (Pt 2), 181-182.

Crawford, J.R., Stewart, L.E., & Moore, J.W. (1989). Demonstration of savings on the AVLT and development of a parallel form. J Clin Exp Neuropsychol, 11(6), 975-981.

Crawford, J.R., Moore, J.W., & Cameron, I.M. (1992). Verbal fluency: a NART-based equation for the estimation of premorbid performance. Br J Clin Psychol, 31 (Pt 3), 327-329.

Crawford, J.R., Gray, C.D., & Allan, K.M. (1995). The WAIS-R(UK): basic psychometric properties in an adult UK sample. Br J Clin Psychol, 34 (Pt 2), 237-250.

Crinella, F.M., Beck, F.W., & Robinson, J.W. (1971). Unilateral dominance is not related to neuropsychological integrity. Child Dev, 42(6), 2033-2054.

Crow, T.J., & Done, D.J. (1992). Prenatal exposure to influenza does not cause schizophrenia. Br J Psychiatry, 161, 390-393.

Crow, T.J. (1997). Is schizophrenia the price that Homo sapiens pays for language? Schizophr Res, 28(2-3), 127-141.

Cutting, J. (1985). The Psychology of Schizophrenia. Edinburgh: Churchill Livingstone.

Dalman, C., Allebeck, P., Cullberg, J., Grunewald, C., & Koster, M. (1999). Obstetric complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. Arch Gen Psychiatry, 56(3), 234-240.

Das, J.P. (1970). Changes in Stroop-Test responses as a function of mental age. British Journal of Social and Clinical Psychology, (1), 68-73.

David, A.S., Malmberg, A., Brandt, L., Allebeck, P., & Lewis, G. (1997). IQ and risk for schizophrenia: a population-based cohort study. Psychol Med, 27(6), 1311-1323.

Davies, N., Russell, A., Jones, P., & Murray, R.M. (1998). Which characteristics of schizophrenia predate psychosis? J Psychiatr Res, 32(3-4), 121-131.

Davis, W.R. (1985). Coping Resources of Children at Risk for Mental Disorders. The New School for Social Research, New York;

Degreef, G., Ashtari, M., Bogerts, B., Bilder, R.M., Jody, D.N., Alvir, J.M., & Lieberman, J.A. (1992). Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. Arch Gen Psychiatry, 49(7), 531-537.

DeLisi, L.E., Goldin, L.R., Hamovit, J.R., Maxwell, M.E., Kurtz, D., & Gershon, E.S. (1986). A family study of the association of increased ventricular size with schizophrenia. Arch Gen Psychiatry, 43(2), 148-153.

DeLisi, L.E., Dauphinais, I.D., & Gershon, E.S. (1988). Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. Schizophr Bull, 14(2), 185-191.

DeLisi, L.E., Friedrich, U., Wahlstrom, J., Boccio-Smith, A., Forsman, A., Eklund, K., & Crow, T.J. (1994). Schizophrenia and sex chromosome anomalies. Schizophr Bull, 20(3), 495-505.

DeLisi, L.E. (1999). Defining the course of brain structural change and plasticity in schizophrenia. Psychiatry Res, 92(1), 1-9.

Dellatolas, G., Curt, F., & Lellouch, J. (1991). Birth order and month of birth are not related with handedness in a sample of 9370 young men. Cortex, 27(1), 137-140.

Der, G., Gupta, S., & Murray, R.M. (1990). Is schizophrenia disappearing? [see comments]. Lancet, 335(8688), 513-516.

Dohrenwend, B.P., & Dohrenwend, B.S. (1969). Social Status and Psychological Disorder: a Causal Inquiry. New York: John Wiley and Sons.

Dolan, R.J., Fletcher, P.C., McKenna, P., Friston, K.J., & Frith, C.D. (1999). Abnormal neural integration related to cognition in schizophrenia. Acta Psychiatr Scand Suppl, 395, 58-67.

Done, D.J., Johnstone, E.C., Frith, C.D., Golding, J., Shepherd, P.M., & Crow, T.J. (1991). Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample [see comments]. BMJ, 302(6792), 1576-1580.

Done, D.J., Crow, T.J., Johnstone, E.C., & Sacker, A. (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11 [see comments]. BMJ, 309(6956), 699-703.

Doody, G.A., Johnstone, E.C., Sanderson, T.L., Owens, D.G., & Muir, W.J. (1998). 'Pfropfschizophrenie' revisited. Schizophrenia in people with mild learning disability. Br J Psychiatry, 173, 145-153.

Driscoll, R.M. (1984). Intentional and incidental learning in children vulnerable to psychopathology. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 320-326). Cambridge, England UK: Cambridge University Press.

Dryden, R. (1991). Fetal clues to handedness [letter; comment]. Nature, 350(6313), 27

Dunham, H.W. (1965). Community and Schizophrenia: An Epidemiological Analysis. Detroit, Michigan: Wayne State University Press.

Dunkley, G., & Rogers, D. (1994). The cognitive impairment of severe psychiatric illness: A clinical study. In A. S. David, J. C. Cutting, & a. et (Eds.), The neuropsychology of schizophrenia. Brain damage, behaviour and cognition series. (pp. 181-196). Hove, England UK: Lawrence Erlbaum Associates, Inc.

Dunner, D.L. (1987). High-risk studies: the impact of research design on research results. Compr Psychiatry, 28(5), 363-368.

Dvirskii, A.E. (1976). Functional asymmetry of the cerebral hemispheres in clinical types of schizophrenia. Neurosci Behav Physiol, 7(3), 236-239.

Dvirskii, A.E. (1983). [Clinical manifestations of schizophrenia in right and left-handed patients]. Zh Nevropatol Psikhiatr Im S S Korsakova, 83(5), 724-728.

Dyer, F.N. (1973). The Stroop phenomenon and its use in the study of perceptual, cognitive, and response processes. Memory and Cognition, 1, 106-120.

Eagles, J.M., & Whalley, L.J. (1985). Decline in the diagnosis of schizophrenia among first admissions to Scottish mental hospitals from 1969-78. Br J Psychiatry, 146, 151-154.

Eagles, J.M. (1991). The relationship between schizophrenia and immigration. Are there alternatives to psychosocial hypotheses? [see comments] [see comments]. Br J Psychiatry, 159, 783-789.

Eaton, W.W. (1980). A formal theory of selection for schizophrenia. American Journal of Sociology, 86, 149-157.

Elliott, R., & Sahakian, B.J. (1995). The neuropsychology of schizophrenia: relations with clinical and neurobiological dimensions. Psychol Med, 25(3), 581-594.

Elliott, R., McKenna, P.J., Robbins, T.W., & Sahakian, B.J. (1998). Specific neuropsychological deficits in schizophrenic patients with preserved intellectual function. Cognitive Neuropsychology, 3(1), 45-70.

Ellis, S.J., Ellis, P.J., Marshall, E., Windridge, C., & Jones, S. (1998). Is forced dextrality an explanation for the fall in the prevalence of sinistrality with age? A study in northern England. J Epidemiol Community Health, 52(1), 41-44.

Endicott, J., & Spitzer, R.L. (1978). A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry, 35(7), 837-844.

Enns, R.A., & Reddon, J.R. (1998). The factor structure of the Wechsler Adult Intelligence Scale--Revised: One or two but not three factors. Journal of Clinical Psychology, 54(4), 447-459.

Epstein, J.I., Keefe, R.S., Roitman, S.L., Harvey, P.D., & Mohs, R.C. (1996). Impact of neuroleptic medications on continuous performance test measures in schizophrenia. Biol Psychiatry, 39(10), 902-905.

Erber, J.T., Botwinick, J., & Storandt, M. (1981). The impact of memory on age differences in digit symbol performance. J Gerontol, 36(5), 586-590.

Erlenmeyer-Kimling, L., Cornblatt, B., Friedman, D., Marcuse, Y., Rutschmann, J., Simmens, S., & Devi, S. (1982). Neurological, electrophysiological, and attentional deviations in children at risk for schizophrenia. In H. A. Nasrallah & F. A. Henn (Eds.), Schizophrenia as a Brain Disease. (pp. 61-98). New York: Oxford University Press.

Erlenmeyer-Kimling, L., Marcuse, Y., Cornblatt, B., Friedman, D., Rainer, J.D., & Rutschmann, J. (1984). The New York High-Risk Project. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 169-189). Cambridge, England UK: Cambridge University Press.

Erlenmeyer-Kimling, L., & Cornblatt, B. (1984). Biobehavioral risk factors in children of schizophrenic parents. J Autism Dev Disord, 14(4), 357-374.

Erlenmeyer-Kimling, L., Friedman, D., Cornblatt, B., & Jacobsen, R. (1985). Electrodermal recovery data on children of schizophrenic parents. Psychiatry Res, 14(2), 149-161.

Erlenmeyer-Kimling, L. Risk for Schizophrenia: a longitudinal study. Presented at the Laboratory of Psychology and Psychopathology, DIRP/NIMH Third Annual Retreat and Symposium. Research on Schizophrenia: Data, Dogma, and Directions, NIH, Bethesda, Maryland. (1985). Anonymous.

Erlenmeyer-Kimling, L., & Cornblatt, B. (1987). High-risk research in schizophrenia: a summary of what has been learned. J Psychiatr Res, 21(4), 401-411.

Erlenmeyer-Kimling, L., Squires-Wheeler, E., Adamo, U.H., Bassett, A.S., Cornblatt, B.A., Kestenbaum, C.J., Rock, D., Roberts, S.A., & Gottesman, I.I. (1995). The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow- up. Arch Gen Psychiatry, 52(10), 857-865.

Erlenmeyer-Kimling, L., Janal, M., Rock, D., Roberts, S., & Cornblatt, B. The New York High Risk Project: predicting schizophrenia-related psychosis. (1996). Anonymous.

Fairweather, H. (1976). Sex differences in cognition. Cognition, 4, 231-280.

Falkai, P., & Bogerts, B. (1986). Cell loss in the hippocampus of schizophrenics. Eur Arch Psychiatry Neurol Sci, 236(3), 154-161.

Falkai, P., Bogerts, B., & Rozumek, M. (1988). Limbic pathology in schizophrenia: the entorhinal region--a morphometric study. Biol Psychiatry, 24(5), 515-521.

Faraone, S.V., Seidman, L.J., Kremen, W.S., Pepple, J.R., Lyons, M.J., & Tsuang, M.T. (1995). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. J Abnorm Psychol, 104(2), 286-304.

Faraone, S.V., Seidman, L.J., Kremen, W.S., Toomey, R., Pepple, J.R., & Tsuang, M.T. (1999). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study. J Abnorm Psychol, 108(1), 176-181.

Finkelstein, J.R., Cannon, T.D., Gur, R.E., Gur, R.C., & Moberg, P. (1997). Attentional dysfunctions in neuroleptic-naive and neuroleptic-withdrawn schizophrenic patients and their siblings. J Abnorm Psychol, 106(2), 203-212.

Finlayson, M.A., Johnson, K.A., & Reitan, R.M. (1977). Relationship of level of education to neuropsychological measures in brain-damaged and non-brain-damaged adults. J Consult Clin Psychol, 45(4), 536-542.

Fischer, M. (1971). Psychoses in the offspring of schizophrenic monozygotic twins and their normal co-twins. Br J Psychiatry, 118(542), 43-52.

Fish, B. (1975). Biologic antecedents of psychosis in children. Res Publ Assoc Res Nerv Ment Dis, 54, 49-83.

Fish, B. (1977). Neurobiologic antecedents of schizophrenia in children. Evidence for an inherited, congenital neurointegrative defect. Arch Gen Psychiatry, 34(11), 1297-1313.

Fish, B., Marcus, J., Hans, S.L., Auerbach, J.G., & Perdue, S. (1992). Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem Infant Development Study. Arch Gen Psychiatry, 49(3), 221-235.

Fish, B. (1984). Characteristics and sequelae of the neurointegrative disorder in infants at risk for schizophrenia: 1952-1982. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 423-439). Cambridge, England UK: Cambridge University Press.

Fleminger, J.J., Dalton, R., & Standage, K.J. (1977). Age as a factor in the handedness of adults. Neuropsychologia, 15(3), 471-473.

Fleminger, J.J., Dalton, R., & Standage, K.F. (1977). Handedness in psychiatric patients. Br J Psychiatry, 131, 448-452.

Foerster, A., Lewis, S.W., Owen, M.J., & Murray, R.M. (1991). Low birth weight and a family history of schizophrenia predict poor premorbid functioning in psychosis. Schizophr Res, 5(1), 13-20.

Foerster, A., Lewis, S., Owen, M., & Murray, R. (1991). Pre-morbid adjustment and personality in psychosis. Effects of sex and diagnosis. Br J Psychiatry, 158, 171-176.

Foundas, A.L., Leonard, C.M., & Heilman, K.M. (1995). Morphologic cerebral asymmetries and handedness. The pars triangularis and planum temporale [see comments]. Arch Neurol, 52(5), 501-508.

Franke, P., Maier, W., Hain, C., & Klingler, T. (1992). Wisconsin Card Sorting Test: an indicator of vulnerability to schizophrenia? Schizophr Res, 6(3), 243-249.

Franke, P., Maier, W., Hardt, J., Hain, C., & Cornblatt, B.A. (1994). Attentional abilities and measures of schizotypy: their variation and covariation in schizophrenic patients, their siblings, and normal control subjects. Psychiatry Res, 54(3), 259-272.

Freedman, R., Adler, L.E., Waldo, M.C., Pachtman, E., & Franks, R.D. (1983). Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. Biol Psychiatry, 18(5), 537-551.

Freud, S. (1955). The Psychogenesis of a case of homosexuality in a woman. In Anonymous, The Complete Psychological Works of Sigmund Freud (Vol. 18). London: Hogarth.

Friedman, D., Cornblatt, B., Vaughan, H.J., & Erlenmeyer-Kimling, L. (1986). Event-related potentials in children at risk for schizophrenia during two versions of the continuous performance test [published erratum appears in Psychiatry Res 1986 Oct;19(2):175]. Psychiatry Res, 18(2), 161-177.

Frith, C.D. (1984). Schizophrenia, memory, and anticholinergic drugs. J Abnorm Psychol, 93(3), 339-341.

Frith, C.D. (1987). The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. Psychol Med, 17(3), 631-648.

Frith, C.D., Leary, J., Cahill, C., & Johnstone, E.C. (1991). Performance on psychological tests. Demographic and clinical correlates of the results of these tests. Br J Psychiatry Suppl, (13), 26-26.

Frith, C.D. (1992). The Cognitive Neuropsychology of Schizophrenia. Hove: Lawrence Erlbaum.

Frith, C.D. (1995). Functional imaging and cognitive abnormalities. Lancet, 346(8975), 615-620.

Frith, C.D. (1995). The cognitive abnormalities underlying the symptomatology and the disability of patients with schizophrenia. Int Clin Psychopharmacol, 10 Suppl 3, 87-98.

Frith, C.D. (1996). Neuropsychology of schizophrenia, what are the implications of intellectual and experiential abnormalities for the neurobiology of schizophrenia? Br Med Bull, 52(3), 618-626.

Fuster, J.M. (1980). The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe. New York: Raven Press.

Galaburda, A.M., Corsiglia, J., Resen, G.D., & Sherman, G.F. (1987). Planum temporale asymmetry: reappraisal since Geschwind and Levitsky. Neuropsychologia, 25, 853-868.

Gangestad, S.W., Yeo, R.A., Shaw, P.K., Thoma, R., Daniel, W.F., & Korthank, A. (1996). Human leukocyte antigens and hand preferences: preliminary observations. Neuropsychology, 10, 423-428.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, 9, 55-125.

Garmezy, N., & Phipps-Yonas, S. (1984). An early crossroad in research on risk for schizophrenia: The Dorado Beach Conference. In N. F. Watt, E. J. Anthony, L. C. Wynne, & J. E. Rolf (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 6-18). Cambridge, England UK: Cambridge University Press.

Garver, D.L. (1987). Methodological issues facing the interpretation of high-risk studies: biological heterogeneity. Schizophr Bull, 13(3), 525-529.

Geddes, J.R., & Lawrie, S.M. (1995). Obstetric complications and schizophrenia: a meta-analysis. Br J Psychiatry, 167(6), 786-793.

Geddes, J.R., Verdoux, H., Takei, N., Lawrie, S.M., Bovet, P., Eagles, J.M., Heun, R., McCreadie, R.G., McNeil, T.F., O'Callaghan, E., Stober, G., Willinger, U., & Murray, R.M. (1999). Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. Schizophr Bull, 25(3), 413-423.

Geschwind, N., & Behan, P. (1982). Left-handedness: association with immune disease, migraine, and developmental learning disorder. Proc Natl Acad Sci U S A, 79(16), 5097-5100.

Geschwind, N., & Behan, P. (1984). Laterality, hormones and immunity. In N. Geschwind & A. M. Galaburda (Eds.), Cerebral Dominance. (pp. 211-224). Cambridge, Mass: MIT Press.

Geschwind, N., & Galaburda, A.M. (1987). Cerebral lateralisation: biological mechanisms, associations, and pathology. Cambridge, Mass: MIT press.

Gibbons, J.S., Horn, S.H., Powell, J.M., & Gibbons, J.L. (1984). Schizophrenic patients and their families: A survey in a psychiatric service based on a DGH unit. British Journal of Psychiatry, 144, 70-77.

Glahn, D.C., Cannon, T.D., Gur, R.E., Ragland, J.D., & Gur, R.C. (2000). Working memory constrains abstraction in schizophrenia. Biol Psychiatry, 47(1), 34-42.

Glish, M.A., Erlenmeyer-Kimling, L., & Watt, N.F. (1982). Parental assessment of the social and emotional adaptation of children at high risk for schizophrenia. In B. B. Lahey & A. E. Kadzin (Eds.), Advances in Clinical Child Psychology. (pp. 181-218).

Glosser, G., Butters, N., & Kaplan, E. (1977). Visuoperceptual processes in brain damaged patients on the digit symbol substitution test. Int J Neurosci, 7(2), 59-66.

Goldberg, E.M., & Morrison, S.L. (1963). Schizophrenia and social class. British Journal of Psychiatry, 109, 785-802.

Goldberg, E.M., & Bilder, R.M. (1987). Neuropsychological perspectives: retrograde amnesia and executive deficits. In L. Poon (Ed.), Handbook of Memory Assessment of Older Adults. New York: APA Press.

Goldberg, G. (1985). Supplementary motor area structure and function: review and hypothesis. The Behavioral and Brain Sciences, 8, 567-616.

Goldberg, T.E., Ragland, J.D., Torrey, E.F., Gold, J.M., Bigelow, L.B., & Weinberger, D.R. (1990). Neuropsychological assessment of monozygotic twins discordant for schizophrenia [see comments]. Arch Gen Psychiatry, 47(11), 1066-1072.

Goldberg, T.E., Hyde, T.M., Kleinman, J.E., & Weinberger, D.R. (1993). Course of schizophrenia: neuropsychological evidence for a static encephalopathy. Schizophr Bull, 19(4), 797-804.

Golden, C.J. (1978). Stroop Colour and Word Test. Chicago, IL: Stoelting.

Goldfarb, W. (1967). Factors in the development of schizophrenic children: an approach to subclassification. In J. Romano (Ed.), The Origins of Schizophrenia. The Hague: N.V. Drukkerij Trio.

Goldman-Rakic, P.S., Selemon, L.D., & Schwartz, M.L. (1984). Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. Neuroscience, 12(3), 719-743.

Goldstein, G., & Watson, J.R. (1989). Test-retest reliability of the Halstead-Reitan Battery and the WAIS in a neuropsychiatric population. Clinical Neuropsychologist, 3(3), 265-272.

Goldstein, J.M., Seidman, L.J., Santangelo, S., Knapp, P.H., & Tsuang, M.T. (1994). Are schizophrenic men at higher risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions. J Psychiatr Res, 28(6), 483-498.

Goodman, R. (1988). Obstetric complications and schizophrenia [letter]. Br J Psychiatry, 153, 850

Gottesman, I.I., & Shields, J. (1976). A critical review of recent adoption, twin, and family studies of schizophrenia: behavioral genetics perspectives. Schizophr Bull, 2(3), 360-401.

Gottesman, I.I., & Shields, J. (1982). Schizophrenia, the Epigenetic Puzzle. Cambridge: Cambridge University Press.

Gottesman, I.I., & Bertelsen, A. (1989). Confirming unexpressed genotypes for schizophrenia. Risks in the offspring of Fischer's Danish identical and fraternal discordant twins [see comments]. Arch Gen Psychiatry, 46(10), 867-872.

Gottesman, I.I., & Moldin, S.O. (1997). Schizophrenia genetics at the millennium: cautious optimism. Clin Genet, 52 (5), 404-407.

Green, M.F., Satz, P., Soper, H.V., & Kharabi, F. (1987). Relationship between physical anomalies and age at onset of schizophrenia. Am J Psychiatry, 144(5), 666-667.

Green, M.F., Satz, P., Gaier, D.J., Ganzell, S., & Kharabi, F. (1989). Minor physical anomalies in schizophrenia. Schizophr Bull, 15(1), 91-99.

Green, M.F., Satz, P., Smith, C., & Nelson, L. (1989). Is there atypical handedness in schizophrenia? J Abnorm Psychol, 98(1), 57-61.

Green, M.F., Satz, P., & Christenson, C. (1994). Minor physical anomalies in schizophrenia patients, bipolar patients, and their siblings. Schizophr Bull, 20(3), 433-440.

Gualtieri, C.T., Adams, A., Shen, C.D., & Loiselle, D. (1982). Minor physical anomalies in alcoholic and schizophrenic adults and hyperactive and autistic children. Am J Psychiatry, 139(5), 640-643.

Gur, R.C., Ragland, J.D., & Gur, R.E. (1997). Cognitive changes in schizophrenia-a critical look. International Review of Psychiatry, 9, 449-457.

Gur, R.E. (1977). Motoric laterality imbalance in schizophrenia. A possible concomitant of left hemisphere dysfunction. Arch Gen Psychiatry, 34(1), 33-37.

Gureje, O. (1988). Sensorimotor laterality in schizophrenia: which features transcend cultural influences? Acta Psychiatr Scand, 77(2), 188-193.

Guy, J.D., Majorski, L.V., Wallace, C.J., & Guy, M.P. (1983). The incidence of minor physical anomalies in adult male schizophrenics. Schizophr Bull, 9(4), 571-582.

Hafner, H., Maurer, K., Loeffler, W., & et al. (1995). Onset and early course of schizophrenia. In H. Hafner, W. F. Gattaz, & et al. (Eds.), Search for the Causes of Schizophrenia. (pp. 43-66). Berlin: Springer.

Hafner, H., Behrens, S., De Vry, J., & Gattaz, W.F. (1991). An animal model for the effects of estradiol on dopamine-mediated behavior: implications for sex differences in schizophrenia. Psychiatry Res, 38(2), 125-134.

Hafner, H., & an der Heiden, W. (1997). Epidemiology of schizophrenia [see comments]. Can J Psychiatry, 42(2), 139-151.

Hafner, H., Maurer, K., Loffler, W., an der Heiden, W., Munk-Jorgensen, P., Hambrecht, M., & Riecher-Rossler, A. (1998). The ABC Schizophrenia Study: a preliminary overview of the results. Soc Psychiatry Psychiatr Epidemiol, 33(8), 380-386.

Hafner, H., Loffler, W., Maurer, K., Hambrecht, M., & an, d.H. (1999). Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. Acta Psychiatr Scand, 100(2), 105-118.

Hair, J.F., Anderson, R.E., Tatham, R.L., & Black, W.C. (1992). Multivariate Data Analysis. (3 ed.). New York: Macmillan Publishing Company.

Hallett, S., & Green, P. (1983). Possible defects of interhemispheric integration in children of schizophrenics. J Nerv Ment Dis, 171(7), 421-425.

Hallett, S., Quinn, D., & Hewitt, J. (1986). Defective interhemispheric integration and anomalous language lateralization in children at risk for schizophrenia. J Nerv Ment Dis, 174(7), 418-427.

Hans, S.L., Marcus, J., Nuechterlein, K.H., Asarnow, R.F., Styr, B., & Auerbach, J.G. (1999). Neurobehavioral deficits at adolescence in children at risk for schizophrenia: The Jerusalem Infant Development Study. Arch Gen Psychiatry, 56(8), 741-748.

Hans, S.L., & Marcus, J. (1991). Neurobehavioral development of infants at risk for schizophrenia: A review. In E. F. Walker & a. et (Eds.), Schizophrenia: A life-course developmental perspective. Personality, psychopathology, and psychotherapy series, Vol. 18. (pp. 33-57). San Diego, CA, USA: Academic Press, Inc.

Hanson, D.R., Gottesman, I.I., & Heston, L.L. (1976). Some possible childhood indicators of adult schizophrenia inferred from children of schizophrenics. Br J Psychiatry, 129, 142-154.

Hanson, D.R., Gottesman, I.I., & Meehl, P.E. (1977). Genetic theories and the validation of psychiatric diagnoses: implications for the study of children of schizophrenics. J Abnorm Psychol, 86(6), 575-588.

Hanson, D.R., Gottesman, I.I., & Heston, L.L. (1990). Long-range schizophrenia forecasting: Many a slip twixt cup and lip. In J. E. Rolf, A. S. Masten, & a. et (Eds.), Risk and protective factors in the development of psychopathology. (pp. 424-444). New York, NY, USA: Cambridge University Press.

Hardyck, C., & Petrinovich, L.F. (1977). Left-handedness. Psychol Bull, 84(3), 385-404.

Harris, J.G., Adler, L.E., Young, D.A., Cullum, C.M., Rilling, L.M., Cicerello, A., Intemann, P.M., & Freedman, R. (1996). Neuropsychological dysfunction in parents of schizophrenics. Schizophr Res, 20(3), 253-260.

Harrison, G., Owens, D., Holton, A., Neilson, D., & Boot, D. (1988). A prospective study of severe mental disorder in Afro-Caribbean patients. Psychol Med, 18(3), 643-657.

Harrison, G. (1990). Searching for the causes of schizophrenia: the role of migrant studies. Schizophr Bull, 16(4), 663-671.

Harrison, P.J. (1999). The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain, 122 (Pt 4), 593-624.

Harvey, P., Winters, K., Weintraub, S., & Neale, J.M. (1981). Distractibility in children vulnerable to psychopathology. J Abnorm Psychol, 90(4), 298-304.

Harvey, P.D., Weintraub, S., & Neale, J.M. (1985). Span of apprehension deficits in children vulnerable to psychopathology: A failure to replicate. Journal of Abnormal Psychology, 94(3), 410-413.

Hauser, P., Pollock, B., Finkelberg, F., McGrail, S., Voineskos, G., & Seeman, M. (1985). On sinistrality and sex differences in schizophrenia [letter]. Am J Psychiatry, 142(10), 1228

Heinrichs, D.W., & Buchanan, R.W. (1988). Significance and meaning of neurological signs in schizophrenia. Am J Psychiatry, 145(1), 11-18.

Heinrichs, R.W., & Awad, A.G. (1993). Neurocognitive subtypes of chronic schizophrenia. Schizophr Res, 9(1), 49-58.

Heinrichs, R.W., & Zakzanis, K.K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology, 12(3), 426-445.

Hepper, P.G., Shahidullah, S., & White, R. (1990). Origins of fetal handedness [letter] [see comments]. Nature, 347 (6292), 431

Herman, J., Mirsky, A.F., Ricks, N.L., & Gallant, D. (1977). Behavioral and electrographic measures of attention in children at risk for schizophrenia. J Abnorm Psychol, 86(1), 27-33.

Hicks, R.A., Pellegrini, R.J., & Evans, E.A. (1978). Handedness and birth risk. Neuropsychologia, 16(2), 243-245.

Hicks, R.A., Pellegrini, R.J., Evans, E.A., & Moore, J.D. (1979). Birth risk and left-handedness reconsidered. Arch Neurol, 36(2), 119-120.

Hodges, A., Byrne, M., Grant, E., & Johnstone, E. (1999). People at risk of schizophrenia. Sample characteristics of the first 100 cases in the Edinburgh High-Risk Study. Br J Psychiatry, 174, 547-553.

Hoff, A.L., Riordan, H., O'Donnell, D.W., & DeLisi, L.E. (1991). Cross-sectional and longitudinal neuropsychological test findings in first episode schizophrenic patients. Schizophr Res, 5(3), 197-198.

Hoff, A.L., Riordan, H., O'Donnell, D.W., Morris, L., & DeLisi, L.E. (1992). Neuropsychological functioning of first-episode schizophreniform patients. Am J Psychiatry, 149(7), 898-903.

Hoff, A.L., Sakuma, M., Wieneke, M., Horon, R., Kushner, M., & DeLisi, L.E. (1999). Longitudinal neuropsychological follow-up study of patients with first- episode schizophrenia. Am J Psychiatry, 156(9), 1336-1341.

Holzman, P.S., Proctor, L.R., & Hughes, D.W. (1973). Eye-tracking patterns in schizophrenia. Science, 181(95), 179-181.

Holzman, P.S., Proctor, L.R., Levy, D.L., Yasillo, N.J., Meltzer, H.Y., & Hurt, S.W. (1974). Eye-tracking dysfunctions in schizophrenic patients and their relatives. Arch Gen Psychiatry, 31(2), 143-151.

Holzman, P.S., Solomon, C.M., Levin, S., & Waternaux, C.S. (1984). Pursuit eye movement dysfunctions in schizophrenia. Family evidence for specificity. Arch Gen Psychiatry, 41(2), 136-139.

Hubbard, J.I. (1971). Handedness not a function of birth order. Nature, 232(5308), 276-277.

Hultman, C.M., Sparen, P., Takei, N., Murray, R.M., & Cnattingius, S. (1999). Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. BMJ, 318(7181), 421-426.

Hutchinson, G., Takei, N., Fahy, T.A., Bhugra, D., Gilvarry, C., Moran, P., Mallett, R., Sham, P., Leff, J., & Murray, R.M. (1996). Morbid risk of schizophrenia in first-degree relatives of white and African-Caribbean patients with psychosis. Br J Psychiatry, 169(6), 776-780.

Hutton, S.B., Puri, B.K., Duncan, L.J., Robbins, T.W., Barnes, T.R., & Joyce, E.M. (1998). Executive function in first-episode schizophrenia. Psychol Med, 28(2), 463-473.

Hyde, T.M., Nawroz, S., Goldberg, T.E., Bigelow, L.B., Strong, D., Ostrem, J.L., Weinberger, D.R., & Kleinman, J.E. (1994). Is there cognitive decline in schizophrenia? A cross-sectional study. Br J Psychiatry, 164(4), 494-500.

Iacono, W.G. (1985). Psychophysiologic markers of psychopathology: a review. Candian Journal of Psychology, 26, 96-112.

Ingraham, L.J., Kugelmass, S., Frenkel, E., Nathan, M., & Mirsky, A.F. (1995). Twenty-five-year followup of the Israeli High-Risk Study: current and lifetime psychopathology. Schizophr Bull, 21(2), 183-192.

Itil, T.M., Hsu, W., Saletu, B., & Mednick, S. (1974). Computer EEG and auditory evoked potential investigations in children at high risk for schizophrenia. Am J Psychiatry, 131(8), 892-900.

Iversen, L.L. (1979). The chemistry of the brain. Scientific America, 241, 134-149.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J.E., Day, R., & Bertelsen, A. (1992). Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study [published erratum appears in Psychol Med Monogr Suppl 1992 Nov;22(4):following 1092]. Psychol Med Monogr Suppl, 20, 1-97.

Jablensky, A., Hugler, H., Von Cranach, M., & Kalinov, K. (1993). Kraepelin revisited: a reassessment and statistical analysis of dementia praecox and manic-depressive insanity in 1908. Psychol Med, 23(4), 843-858.

Jablensky, A. (1995). Schizophrenia: recent epidemiologic issues. Epidemiol Rev, 17(1), 10-20.

Jablensky, A. (1997). The 100-year epidemiology of schizophrenia. Schizophr Res, 28(2-3), 111-125.

Jablensky, A., & Cole, S.W. (1997). Is the earlier age at onset of schizophrenia in males a confounded finding? Results from a cross-cultural investigation [see comments]. Br J Psychiatry, 170, 234-240.

Jakob, H., & Beckmann, H. (1986). Prenatal developmental disturbances in the limbic allocortex in schizophrenics. J Neural Transm, 65(3-4), 303-326.

Jaskiw, G.E., & Weinberger, D.R. (1992). Dopamine and schizophrenia: a cortically corrective perspectve. Seminars in the Neurosciences, 4, 179-188.

Jeste, D.V., & Lohr, J.B. (1989). Hippocampal pathologic findings in schizophrenia. A morphometric study. Arch Gen Psychiatry, 46(11), 1019-1024.

Johnstone, E.C., Crow, T.J., Frith, C.D., Husband, J., & Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet, 2(7992), 924-926.

Johnstone, E.C., Owens, D.G., Crow, T.J., Frith, C.D., Alexandropolis, K., Bydder, G., & Colter, N. (1989). Temporal lobe structure as determined by nuclear magnetic resonance in schizophrenia and bipolar affective disorder. J Neurol Neurosurg Psychiatry, 52(6), 736-741.

Johnstone, E.C. (1991). The Harrow (1975-1985) study of the disabilities and circumstances of schizophrenic patients. British Journal of Psychiatry, 159(Supplement 13)

Johnstone, E.C., Abukmeil, S.S., Byrne, M., Clafferty, R., Grant, E., Hodges, A., Lawrie, S.M., & Owens, D.G. (in press). Edinburgh high risk study -Findings after four years: demographic, attainment, and psychopathological issues. Schizophr Res.

Jones, P., & Murray, R.M. (1991). The genetics of schizophrenia is the genetics of neurodevelopment. Br J Psychiatry, 158, 615-623.

Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet, 344(8934), 1398-1402.

Jones, P., & Done, D.J. (1997). From birth to onset: a developmental perspective of schizophrenia in two national birth cohorts. In M. S. Keshaven & R. M. Murray (Eds.), Neurodevelopmental Models of Psychopathology. (pp. 119-136). Cambridge: Cambridge University Press.

Joseph, A.B. (1990). Non-right-handedness and maleness correlate with tardive dyskinesia among patients taking neuroleptics. Acta Psychiatr Scand, 81(6), 530-533.

Josiassen, R.C., Shagass, C., Roemer, R.A., & Straumanis, J.J. (1985). Attention-related effects on somatosensory evoked potentials in college students at high risk for psychopathology. J Abnorm Psychol, 94(4), 507-518.

Kameyama, T., Niwa, S.-I., Hiramatsu, S.-I., & Saitoh, D. (1983). Hand Preference and Eye Dominance Patterns in Japanese Schizophrenics. In P. Flor-Henry & J. Gruzelier (Eds.), Laterality and Psychopathology. (pp. 163-180). Amsterdam: Elsevier.

Katsanis, J., & Iacono, W.G. (1989). Association of left-handedness with ventricle size and neuropsychological performance in schizophrenia [see comments]. Am J Psychiatry, 146(8), 1056-1058.

Kaufman, A.S. (1979). Intelligent Testing with the WISC-R. New York: John Wiley and sons.

Kaufman, A.S., McLean, J.E., & Reynolds, C.R. (1988). Sex, race, residence, region, and education differences on the 11 WAIS- R subtests. J Clin Psychol, 44(2), 231-248.

Kaufman, A.S., McLean, J.E., & Reynolds, C.R. (1991). Analysis of WAIS-R factor patterns by sex and race. J Clin Psychol, 47(4), 548-557.

Keefe, R.S., Silverman, J.M., Roitman, S.E., Harvey, P.D., Duncan, M.A., Alroy, D., Siever, L.J., Davis, K.L., & Mohs, R.C. (1994). Performance of nonpsychotic relatives of schizophrenic patients on cognitive tests. Psychiatry Res, 53(1), 1-12.

Keilp, J.G., Herrera, J., Stritzke, P., & Cornblatt, B.A. (1997). The continuous performance test, identical pairs version (CPT-IP): III. Brain functioning during performance of numbers and shapes subtasks [In Process Citation]. Psychiatry Res, 74(1), 35-45.

Kemali, D., Maj, M., Galderisi, S., Milici, N., & Salvati, A. (1989). Ventricle-to-brain ratio in schizophrenia: a controlled follow-up study. Biol Psychiatry, 26(7), 756-759.

Kendell, R.E., & Kemp, I.W. (1989). Maternal influenza in the etiology of schizophrenia [see comments]. Arch Gen Psychiatry, 46(10), 878-882.

Kendler, K.S., Gruenberg, A.M., & Strauss, J.S. (1981). An independent analysis of the Copenhagen sample of the Danish adoption study of schizophrenia. II. The relationship between schizotypal personality disorder and schizophrenia. Arch Gen Psychiatry, 38(9), 982-984.

Kendler, K.S., Gruenberg, A.M., & Strauss, J.S. (1981). An independent analysis of the Copenhagen sample of the Danish adoption study of schizophrenia. III. The relationship between paranoid psychosis (delusional disorder) and the schizophrenia spectrum disorders. Arch Gen Psychiatry, 38(9), 985-987.

Kendler, K.S., & Gruenberg, A.M. (1984). An independent analysis of the Danish Adoption Study of Schizophrenia. VI. The relationship between psychiatric disorders as defined by DSM- III in the relatives and adoptees. Arch Gen Psychiatry, 41(6), 555-564.

Kendler, K.S., & Eaves, L.J. (1986). Models for the joint effect of genotype and environment on liability to psychiatric illness. Am J Psychiatry, 143(3), 279-289.

Kendler, K.S. (1986). The genetics of schizophrenia: a current perspective. Psychopharmacol Bull, 22(3), 918-922.

Kendler, K.S., Lieberman, J.A., & Walsh, D. (1989). The Structured Interview for Schizotypy (SIS): a preliminary report. Schizophr Bull, 15(4), 559-571.

Kendler, K.S., Gruenberg, A.M., & Kinney, D.K. (1994). Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. Arch Gen Psychiatry, 51(6), 456-468.

Kennard, M.A. (1960). Value of equivocal signs in neurologic diagnosis. Neurology, 10, 753-764.

Kety, S.S., Rosenthal, D., Wender, P.H., Schulsinger, F., & Jacobsen, B. (1975). Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: a preliminary report based on psychiatric interviews. Proc Annu Meet Am Psychopathol Assoc, (63), 147-165.

Kety, S.S., Rosenthal, D., Wender, P.H., Schulsinger, F., & Jacobsen, B. (1976). Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic. Behav Genet, 6(3), 219-225.

Kety, S.S. (1983). Mental illness in the biological and adoptive relatives of schizophrenic adoptees: findings relevant to genetic and environmental factors in etiology. Am J Psychiatry, 140(6), 720-727.

Kety, S.S. (1987). The significance of genetic factors in the etiology of schizophrenia: results from the national study of adoptees in Denmark. J Psychiatr Res, 21(4), 423-429.

Kety, S.S. (1988). Schizophrenic illness in the families of schizophrenic adoptees: findings from the Danish national sample. Schizophr Bull, 14(2), 217-222.

Kety, S.S., & Ingraham, L.J. (1992). Genetic transmission and improved diagnosis of schizophrenia from pedigrees of adoptees. J Psychiatr Res, 26(4), 247-255.

Kety, S.S., Wender, P.H., Jacobsen, B., Ingraham, L.J., Jansson, L., Faber, B., & Kinney, D.K. (1994). Mental illness in the biological and adoptive relatives of schizophrenic adoptees. Replication of the Copenhagen Study in the rest of Denmark. Arch Gen Psychiatry, 51(6), 442-455.

Kim, D., Raine, A., Triphon, N., & Green, M.F. (1992). Mixed handedness and features of schizotypal personality in a nonclinical sample. J Nerv Ment Dis, 180(2), 133-135.

Kinney, D.K., & Jacobsen, B. (1978). Environmental factors in schizophrenia: new adoption study evidence. In L. C. Wynne, R. L. Cromwell, & S. Matthysse (Eds.), The Nature of Schizophrenia: New Approaches to Research and Treatment. New York: John Wiley and Sons.

Klienbaum, D.G., Kupper, L.L., Muller, K.E., & Nizam, A. (1998). Applied Regression Analysis and Other Multivariate Methods. (3 ed.). Pacific Grove, California: Brooks/Cole Publishing Company.

Kohn, M.L. (1968). Social class and schizophrenia: A critical review. In D. Rosenthal & S. S. Kety (Eds.), The Transmission of Schizophrenia. (pp. 155-173). Oxford: Pergamon Press.

Kohn, M.L. (1973). Social class and schizophrenia: a critical review and a reformulation. Schizophr Bull, 7, 60-79.

Kohn, M.L. (1976). The interaction of social class and other factors in the etiology of schizophrenia. Am J Psychiatry, 133(2), 177-180.

Kolakowska, T., Williams, A.O., Jambor, K., & Ardern, M. (1985). Schizophrenia with good and poor outcome. III: Neurological 'soft' signs, cognitive impairment and their clinical significance. Br J Psychiatry, 146, 348-357.

Kovelman, J.A., & Scheibel, A.B. (1984). A neurohistological correlate of schizophrenia. Biol Psychiatry, 19(12), 1601-1621.

Kremen, W.S., Seidman, L.J., Faraone, S.V., Pepple, J.R., & Tsuang, M.T. (1992). Attention/information-processing factors in psychotic disorders. Replication and extension of recent neuropsychological findings. J Nerv Ment Dis, 180(2), 89-93.

Kremen, W.S., Seidman, L.J., Pepple, J.R., Lyons, M.J., Tsuang, M.T., & Faraone, S.V. (1994). Neuropsychological risk indicators for schizophrenia: a review of family studies. Schizophr Bull, 20(1), 103-119.

Kremen, W.S., Goldstein, J.M., Seidman, L.J., Toomey, R., Lyons, M.J., Tsuang, M.T., & Faraone, S.V. (1997). Sex differences in neuropsychological function in non-psychotic relatives of schizophrenic probands. Psychiatry Res, 66(2-3), 131-144.

Kremen, W.S., Buka, S.L., Seidman, L.J., Goldstein, J.M., Koren, D., & Tsuang, M.T. (1998). IQ decline during childhood and adult psychotic symptoms in a community sample: a 19-year longitudinal study. Am J Psychiatry, 155(5), 672-677.

Kringlen, E. (1991). Adoption studies in functional psychosis [editorial]. Eur Arch Psychiatry Clin Neurosci, 240(6), 307-313.

Kugelmass, S., Faber, N., Ingraham, L.J., Frenkel, E., Nathan, M., Mirsky, A.F., & Ben Shakhar, G. (1995). Reanalysis of SCOR and anxiety measures in the Israeli High-Risk Study. Schizophr Bull, 21(2), 205-217.

Kunugi, H., Nanko, S., & Takei, N. (1992). Influenza and schizophrenia in Japan [letter; comment]. Br J Psychiatry, 161, 274-275.

Laing, R.D., & Esterson, A. (1967). Families and schizophrenia. Int J Psychiatry, 4(1), 65-71.

Lal, R., & Sharma, S. (1987). Minor physical anomalies in schizophrenia. Indian Journal of Psychiatry, 29(119), 122

Landau, R., Harth, P., Othnay, N., & Sharfhertz, C. (1972). The influence of psychotic parents on their children's development. Am J Psychiatry, 129(1), 38-43.

Lane, A., Byrne, M., Mulvany, F., Kinsella, A., Waddington, J.L., Walsh, D., Larkin, C., & O'Callaghan, E. (1995). Reproductive behaviour in schizophrenia relative to other mental disorders: evidence for increased fertility in men despite decreased marital rate. Acta Psychiatr Scand, 91(4), 222-228.

Lane, A., Colgan, K., Moynihan, F., Burke, T., Waddington, J.L., Larkin, C., & O'Callaghan, E. (1996). Schizophrenia and neurological soft signs: gender differences in clinical correlates and antecedent factors. Psychiatry Res, 64(2), 105-114.

Lane, A., Kinsella, A., Murphy, P., Byrne, M., Keenan, J., Colgan, K., Cassidy, B., Sheppard, N., Horgan, R., Waddington, J.L., Larkin, C., & O'Callaghan, E. (1997). The anthropometric assessment of dysmorphic features in schizophrenia as an index of its developmental origins. Psychol Med, 27(5), 1155-1164.

Lansky, L.M., Feinstein, H., & Peterson, J.M. (1988). Demography of handedness in two samples of randomly selected adults (N = 2083). Neuropsychologia, 26(3), 465-477.

Larroche, J.L. (1984). Malformations of the Nervous System. In J. M. Adams & et al. (Eds.), Greenfields Neuropathology. (pp. 385-403). London: Edward Arnold.

Laurent, A., Saoud, M., Bougerol, T., d'Amato, T., Anchisi, A.M., Biloa-Tang, M., Dalery, J., & Rochet, T. (1999). Attentional deficits in patients with schizophrenia and in their non- psychotic first-degree relatives [In Process Citation]. Psychiatry Res, 89(3), 147-159.

Lawrie, S.M., Whalley, H., Kestelman, J.N., Abukmeil, S.S., Byrne, M., Hodges, A., Rimmington, J.E., Best, J.J., Owens, D.G., & Johnstone, E.C. (1999). Magnetic

resonance imaging of brain in people at high risk of developing schizophrenia [see comments]. Lancet, 353(9146), 30-33.

Le Fever, F.F. (1985). A noncoding motoric equivalent measures most of what the digit symbol does, including age changes. Percept Mot Skills, 61(2), 371-377.

Lea, M. (1986). A British Supplement to the Manual for the Wechsler Adult Intelligence Scale-Revised. San Antonio, Texas: Psychological Corporation.

Leng, N.R., & Parkin, A.J. (1990). The assessment of memory disorders: A review of some current clinical tests. Clinical Rehabilitation, 4(2), 159-165.

Lenzenweger, M.F., Cornblatt, B.A., & Putnick, M. (1991). Schizotypy and sustained attention. J Abnorm Psychol, 100 (1), 84-89.

Levin, S., Yurgelun-Todd, D., & Craft, S. (1989). Contributions of clinical neuropsychology to the study of schizophrenia. J Abnorm Psychol, 98(4), 341-356.

Leviton, A., & Kilty, T. (1976). Letter: Birth order and left-handedness. Arch Neurol, 33(9), 664

Levy, D.L., Holzman, P.S., Matthysse, S., & Mendell, N.R. (1994). Eye tracking and schizophrenia: a selective review. Schizophr Bull, 20(1), 47-62.

Levy, J., & Nagylaki, T. (1972). A model for the genetics of handedness. Genetics, 72(1), 117-128.

Levy, J. (1976). A review of evidence for a genetic component in the determination of handedness. Behav Genet, 6(4), 429-453.

Levy, J., & Gur, R.E. (1980). Individual differences in psychoneurological organisation. In J. Herron (Ed.), Neuropsychology of Left Handedness. (pp. 203 Ney York: Academic Press.

Lewine, R.R.J., Watt, N.F., & Grubb, T.W. (1984). High-risk-for-schizophrenia research: Sampling bias and its implications. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 557-571). Cambridge, England UK: Cambridge University Press.

Lewine, R.R.J. (1984). Stalking the schizophrenia marker: Evidence for a general vulnerability model of psychopathology. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 545-550). Cambridge, England UK: Cambridge University Press.

Lewis, M.S. (1989). Age incidence and schizophrenia: Part I. The season of birth controversy [see comments]. Schizophr Bull, 15(1), 59-73.

Lewis, S.W., & Murray, R.M. (1987). Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. J Psychiatr Res, 21(4), 413-421.

Lewis, S.W. (1989). Congenital risk factors for schizophrenia. Psychol Med, 19(1), 5-13.

Lewis, S.W. (1990). Computerised tomography in schizophrenia 15 years on [see comments]. Br J Psychiatry Suppl, (9), 16-24.

Lewis, S.W., Owen, M.J., & Murray, R.M. (1989). Obstetric complications and schizophrenia: Methodology and mechanisms. In S. C. Schulz & C. A. Tamminga

(Eds.), Schizophrenia: Scientific progress. (pp. 56-68). New York, NY, USA: Oxford University Press.

Lezak, M.D. (1995). Neuropsychological Assessment (3rd ed.). New York, NY, USA: Oxford University Press.

Liddle, P.F. (1987). The symptoms of chronic schizophrenia. A re-examination of the positive- negative dichotomy [see comments]. Br J Psychiatry, 151, 145-151.

Liddle, P.F. (1987). Schizophrenic syndromes, cognitive performance and neurological dysfunction. Psychol Med, 17(1), 49-57.

Liddle, P.F., & Morris, D.L. (1991). Schizophrenic syndromes and frontal lobe performance. Br J Psychiatry, 158, 340-345.

Lidz, T., Cornelison, A.R., Singer, M.T., Schafer, S., & Fleck, S. (1965). The mothers of schizophrenic patients. In T. Lidz, S. Fleck, & A. Cornelison (Eds.), Schizophrenia and the Family. New York:

Liederman, J. (1983). Mechanisms underlying instability in the development of hand preferences. In J. Young, S. J. Segalowitz, C. M. Carter, & S. E. Trehub (Eds.), Manual Specialization and the Developing Brain. New York: Academic Press.

Lifshitz, M., Kugelmass, S., & Karov, M. (1985). Perceptual-motor and memory performance of high-risk children. Schizophr Bull, 11(1), 74-84.

Lishman, W.A., & McMeekan, E.R. (1976). Hand preference patterns in psychiatric patients. Br J Psychiatry, 129, 158-166.

Long, C.J., & Brown, D.A. Analysis of temporal cortex dysfunction by neuropschological techniques. Presented at the annual convention of the American Psychological association, New York. (un pub)

Luria, A.R. (1970). The functional organization of the brain. Sci Am, 222(3), 66-72.

Lyon, M., Barr, C.E., Cannon, T.D., Mednick, S.A., & Shore, D. (1989). Fetal neural development and schizophrenia [clinical conference]. Schizophr Bull, 15(1), 149-161.

Lyons, M.J., Toomey, R., Seidman, L.J., Kremen, W.S., Faraone, S.V., & Tsuang, M.T. (1995). Verbal learning and memory in relatives of schizophrenics: preliminary findings. Biol Psychiatry, 37(10), 750-753.

Macartney-Filgate, M.S., & Vriezen, E.R. (1988). Intercorrelation of clinical tests of verbal memory. Archives of Clinical Neuropsychology, 3(2), 121-126.

Mahurin, R.K., Velligan, D.I., & Miller, A.L. (1998). Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. Psychiatry Res, 79(2), 139-149.

Malec, J.F., Ivnik, R.J., Smith, G.E., & Tangalos, E.G. (1992). Mayo's Older Americans Normative Studies: Utility of corrections for age and education for the WAIS--R. Clinical Neuropsychologist, 6(Suppl), 31-47.

Malesu, R.R., Cannon, M., Jones, P.B., McKenzie, K., Gilvarry, K., Rifkin, L., Toone, B.K., & Murray, R.M. (1996). Mixed-handedness in patients with functional psychosis. Br J Psychiatry, 168(2), 234-236.

Malla, A.K., Cortese, L., Shaw, T.S., & Ginsberg, B. (1990). Life events and relapse in schizophrenia. A one year prospective study. Soc Psychiatry Psychiatr Epidemiol, 25(4), 221-224.

Manoach, D.S., Maher, B.A., & Manschreck, T.C. (1988). Left-handedness and though disorder in the schizophrenias. J Abnorm Psychol, 97(1), 97-99.

Manoach, D.S. (1994). Handedness is related to formal thought disorder and language dysfunction in schizophrenia. J Clin Exp Neuropsychol, 16(1), 2-14.

Marcus, J., Hans, S.L., Nagler, S., Auerbach, J.G., Mirsky, A.F., & Aubrey, A. (1987). Review of the NIMH Israeli Kibbutz-City Study and the Jerusalem Infant Development Study. Schizophr Bull, 13 (3), 425-438.

Marcus, J., Auerbach, J., Wilkinson, L., & Burack, C.M. (1984). Infants at risk for schizophrenia: The Jerusalem Infant Development Study. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 440-464). Cambridge, England UK: Cambridge University Press.

Markow, T.A., & Wandler, K. (1986). Fluctuating dermatoglyphic asymmetry and the genetics of liability to schizophrenia. Psychiatry Res, 19(4), 323-328.

Markow, T.A., & Gottesman, I.I. (1989). Fluctuating dermatoglyphic asymmetry in psychotic twins. Psychiatry Res, 29 (1), 37-43.

Markow, T.A., & Gottesman, I.I. (1989). Dermatoglyphic fluctuating asymmetry in twins and singletons. Hereditas, 110(3), 211-215.

Marlow, N., Roberts, B.L., & Cooke, R.W. (1989). Laterality and prematurity. Arch Dis Child, 64(12), 1713-1716.

Matarazzo, J.D., & Herman, D.O. (1984). Base rate data for the WAIS-R: test-retest stability and VIQ-PIQ differences. J Clin Neuropsychol, 6(4), 351-366.

McCaffrey, R.J., Ortega, A., Orsillo, S.M., & Nelles, W.B. (1992). Practice effects in repeated neuropsychological assessments. Clinical Neuropsychologist, 6(1), 32-42.

McConaghy, N. (1959). The use of an object sorting test in elucidating the hereditary factor in schizophrenia. Journal of Neurosurgery and Psychiatry, 22, 243-246.

McFie, J. (1960). Psychological testing in clinical neurology. Journal of Nervous and Mental Diseases, 131, 383-393.

McFie, J. (1975). Assessment of Organic Intellectual Impairment. London: Academic Press.

McGrath, J.J., Pemberton, M.R., Welham, J.L., & Murray, R.M. (1994). Schizophrenia and the influenza epidemics of 1954, 1957 and 1959: a southern hemisphere study. Schizophr Res, 14(1), 1-8.

McGue, M., Gottesman, I.I., & Rao, D.C. (1985). Resolving genetic models for the transmission of schizophrenia. Genet Epidemiol, 2(1), 99-110.

McGuffin, P., Farmer, A., & Gottesman, I.I. (1987). Is there really a split in schizophrenia? The genetic evidence. Br J Psychiatry, 150, 581-592.

McGuffin, P., Farmer, A., & Harvey, I. (1991). A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system [news]. Arch Gen Psychiatry, 48(8), 764-770.

McGuffin, P., Owen, M.J., O'Donovan, M.C., Thapar, A., & Gottesman, I.I. (1994). Seminars in psychiatric genetics. (ix ed.). London, England UK: Gaskell/Royal College of Psychiatrists.

McGuire, P.K., & Frith, C.D. (1996). Disordered functional connectivity in schizophrenia [editorial]. Psychol Med, 26(4), 663-667.

McKenna, P., Clare, L., & Baddeley, A.D. (1995). Schizophrenia. In A. D. Baddeley, B. A. Wilson, & F. N. Watts (Eds.), Handbook of Memory Disorders. (pp. 271-292). Chichester: John Wiley and Sons.

McKenna, P.J., Tamlyn, D., Lund, C.E., Mortimer, A.M., Hammond, S., & Baddeley, A.D. (1990). Amnesic syndrome in schizophrenia. Psychol Med, 20(4), 967-972.

McManus, I.C. (1984). Genetics of handedness in relation to language disorder. Adv Neurol, 42, 125-138.

McManus, I.C. (1985). Handedness, language dominance and aphasia: a genetic model. Psychol Med Monogr Suppl, 8, 1-40.

McManus, I.C., & Bryden, M.P. (1991). Geschwind's theory of cerebral lateralization: developing a formal, causal model. Psychol Bull, 110(2), 237-253.

McManus, I.C. (1991). The inheritance of left-handedness. Ciba Found Symp, 162, 251-267.

McNeil, T.F., & Kaij, L. (1974). Reproduction among female mental patients: obstetric complications and physical size of offspring. Acta Psychiatr Scand, 50(1), 3-15.

McNeil, T.F., & Kaij, L. (1978). Obstetric factors in the development of schizophrenia: complications in the births of preschizophrenics and in reproductions by schizophrenic parents. In L. C. Wynne, R. L. Cromwell, & S. Matthysse (Eds.), The Nature of Schizophrenia: A New Approach to Research and Treatments. (pp. 401-429). New York: Wiley.

McNeil, T.F., & Kaij, L. (1979). Etiological relevance of comparisons of high-risk and low-risk groups. Acta Psychiatr Scand, 59(5), 545-560.

McNeil, T.F. (1988). Obstetric factors and perinatal injuries. In M. T. Tsuang & J. C. Simpson (Eds.), Handbook of Schizophrenia, Vol 3. Nosology, Epidemiology, and Genetics. (pp. 319-344). Amsterdam: Eslevier.

Mednick, S., & Schulsinger, F. (1968). Some premorbid characteristics relating to breakdown in children with schizophrenic mothers. In D. Rosenthal & S. S. Kety (Eds.), The Transmission of Schizophrenia. (pp. 267-291). Oxford: Pergamon Press.

Mednick, S.A., Schulsinger, F., Teasdale, T.W., Schulsinger, H., Venables, P., & Rock, D.R. (1978). Schizophrenia in high-risk children: sex differences in predisposing factors. In Serban G. (Ed.), Cognitive Defects in the Development of Mental Illness. (pp. 169-197). New York: Brunner/ Mazel.

Mednick, S.A., Parnas, J., & Schulsinger, F. (1987). The Copenhagen High-Risk Project, 1962-86. Schizophr Bull, 13(3), 485-495.

Mednick, S.A., Machon, R.A., Huttunen, M.O., & Bonett, D. (1988). Adult schizophrenia following prenatal exposure to an influenza epidemic. Arch Gen Psychiatry, 45(2), 189-192.

Mednick, S.A., Huttunen, M.O., & Machon, R.A. (1994). Prenatal influenza infections and adult schizophrenia. Schizophr Bull, 20(2), 263-267.

Meehl, P.E. (1957). When shall we use our heads instead of the formula. Journal of Counseling Psychology, 4, 268-272.

Meehl, P.E. (1973). Psychodiagnosis: Selected Papers. Minneapolis: University of Minnesota.

Mellor, C.S. (1992). Dermatoglyphic evidence of fluctuating asymmetry in schizophrenia [see comments]. Br J Psychiatry, 160, 467-472.

Mellsop, G. (1973). Adult psychiatric patients on whom information was recorded during childhood. Br J Psychiatry, 123(577), 703-710.

Merrin, E.L. (1984). Motor and sighting dominance in chronic schizophrenics. Relationship to social competence, age at first admission, and clinical course. Br J Psychiatry, 145, 401-406.

Merritt, R.D., & Balogh, D.W. (1984). The use of a backward masking paradigm to assess information-processing deficits among schizotypics. A re-evaluation of Steronko and Woods. J Nerv Ment Dis, 172(4), 216-224.

Miklowitz, D.J., Strachan, A.M., Goldstein, M.J., Doane, J.A., Snyder, K.S., Hogarty, G.E., & Falloon, I.R. (1986). Expressed emotion and communication deviance in the families of schizophrenics. J Abnorm Psychol, 95(1), 60-66.

Mirsky, A.F. (1988). The Israeli High-Risk Study. In D. L. Dunner, E. S. Gershon, & J.-E. Barrett (Eds.), Relatives at Risk for Mental Disorder. (pp. 279-296). New York: Raven Press.

Mirsky, A.F., Lochhead, S.J., Jones, B.P., Kugelmass, S., Walsh, D., & Kendler, K.S. (1992). On familial factors in the attentional deficit in schizophrenia: a review and report of two new subject samples. J Psychiatr Res, 26(4), 383-403.

Mirsky, A.F., Yardley, S.L., Jones, B.P., Walsh, D., & Kendler, K.S. (1995). Analysis of the attention deficit in schizophrenia: a study of patients and their relatives in Ireland. J Psychiatr Res, 29(1), 23-42.

Mishler, E.G., & Waxler, N.E. (1965). Family interaction processes and schizophrenia: a review of current theories. Merrill-Palmer Quarterly, 11, 269

Mitchell, A., & Wainwright, P.E. (1994). Bias in the design of studies which examine genetic and environmental influences on behaviour. Can J Public Health, 85(3), 212-215.

Mockler, D., Riordan, J., & Sharma, T. (1997). Memory and intellectual deficits do not decline with age in schizophrenia. Schizophr Res, 26(1), 1-7.

Mohamed, S., Paulsen, J.S., O'Leary, D., Arndt, S., & Andreasen, N. (1999). Generalized cognitive deficits in schizophrenia: a study of first- episode patients. Arch Gen Psychiatry, 56(8), 749-754.

Moldin, S.O., & Gottesman, I.I. (1997). At issue: genes, experience, and chance in schizophrenia--positioning for the 21st century. Schizophr Bull, 23(4), 547-561.

Morgan, M.J., & Corballis, M.C. (1978). On the biological basis of human laterality: II. The mechanisms of inheritance. Behavioral and Brain Sciences, 1(2), 270-336.

Morris, M., Cotter, D., Takei, N., & et al. (1993). An Association between schizophrenic births and influenza deaths in Ireland in the Years 1921- 1971 [Abstract]. Schizophr Res, 9, 137

Morrison-Stewart, S.L., Williamson, P.C., Corning, W.C., Kutcher, S.P., Snow, W.G., & Merskey, H. (1992). Frontal and non-frontal lobe neuropsychological test performance and clinical symptomatology in schizophrenia. Psychol Med, 22(2), 353-359.

Mortensen, P.B., Pedersen, C.B., Westergaard, T., Wohlfahrt, J., Ewald, H., Mors, O., Andersen, P.K., & Melbye, M. (1999). Effects of family history and place and season of birth on the risk of schizophrenia [see comments]. N Engl J Med, 340(8), 603-608.

Morton, N.E., & MacLean, C.J. (1974). Analysis of family resemblance. 3. Complex segregation of quantitative traits. Am J Hum Genet, 26(4), 489-503.

Morton, N.E. (1982). Outline of Genetic Epidemiology. Basel: Karger.

Mosher, L.R., Pollin, W., & Stabenau, L.J. (1971). Identical twins discordant for schizophrenia. Arch Gen Psychiatry, 24, 422-430.

Mulvaney, F., O'Callaghan, E., Takei, N., Byrne, M., & Larkin, C. (2000). Does social class of origin influence the risk for later schizophrenia or modify its presentation? Submitted to BMJ,

Munk-Jorgensen, P. (1986). Decreasing first-admission rates of schizophrenia among males in Denmark from 1970 to 1984. Changing diagnostic patterns? Acta Psychiatr Scand, 73(6), 645-650.

Muristein, B.I., & Leipold, W.D. (1961). The role of learning and motor abilities in the Wechsler-Bellevue Digit Symbol test. Educational and Psychological Measurement, 21, 103-112.

Murray, R.M., Lewis, S.W., & Reveley, A.M. (1985). Towards an aetiological classification of schizophrenia. Lancet, 1(8436), 1023-1026.

Murray, R.M., & Lewis, S.W. (1987). Is schizophrenia a neurodevelopmental disorder? [editorial]. Br Med J (Clin Res Ed), 295(6600), 681-682.

Murray, R.M., Jones, P., & O'Callaghan, E. (1991). Fetal brain development and later schizophrenia. Ciba Found Symp, 156, 155-163.

Murray, R.M., O'Callaghan, E., Castle, D.J., & Lewis, S.W. (1992). A neurodevelopmental approach to the classification of schizophrenia. Schizophr Bull, 18(2), 319-332.

Murray, R.M. Developmental insanity or dementia praecox: a new perspective on an old debate. (1996). Anonymous. Leicester University:

Nasrallah, H.A., Keelor, K., Van Schroeder, C., & Whitters, M.M. (1981). Motoric lateralization in schizophrenic males. Am J Psychiatry, 138(8), 1114-1115.

Nasrallah, H.A., Olson, S.C., McCalley-Whitters, M., Chapman, S., & Jacoby, C.G. (1986). Cerebral ventricular enlargement in schizophrenia. A preliminary follow- up study. Arch Gen Psychiatry, 43 (2), 157-159.

Nauta, W.J. (1971). The problem of the frontal lobe: a reinterpretation. J Psychiatr Res, 8(3), 167-187.

Neale, J.M., & Oltmanns, T.F. (1980). Schizophrenia. New York: Wiley.

Neale, J.M. (1982). Information Processing and vulnerability: High-Risk Research. In M. J. Goldstein (Ed.), Preventive Intervention in Schizophrenia: Are We Ready? (pp. 78-89). Washington DC: Superintendent of Docs. US Government Printing Office.

Nelson, H.E., & O'Connell, A. (1978). Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex, 14(2), 234-244.

Nelson, H.E. (1982). The National Adult Reading Test (NART): Test Manual. Windsor, Berks: NFER-Nelson.

Nelson, H.E., Pantelis, C., Carruthers, K., Speller, J., Baxendale, S., & Barnes, T.R. (1990). Cognitive functioning and symptomatology in chronic schizophrenia. Psychol Med, 20(2), 357-365.

Nelson, H.E., & McKenna, P. (1975). The use of current reading ability in the assessment of dementia. British Journal of Social and Clinical Psychology, 14(3), 259-267.

Nelson, L.D., Satz, P., Green, M., & Cicchetti, D. (1993). Re-examining handedness in schizophrenia: now you see it--now you don't. J Clin Exp Neuropsychol, 15(2), 149-158.

Netley, C., & Rovet, J. (1984). Hemispheric lateralization in 47,XXY Klinefelter's syndrome boys. Brain Cogn, 3(1), 10-18.

Newell-Morris, L.L., Fahrenbruch, C.E., & Sackett, G.P. (1989). Prenatal psychological stress, dermatoglyphic asymmetry and pregnancy outcome in the pigtailed macaque (Macaca nemestrina). Biol Neonate, 56(2), 61-75.

Nopoulos, P., Flashman, L., Flaum, M., Arndt, S., & Andreasen, N. (1994). Stability of cognitive functioning early in the course of schizophrenia. Schizophr Res, 14(1), 29-37.

Norton, J.P. (1982). Expressed emotion, affective style, voice tone and communication deviance as predictors of offspring schizophrenia spectrum disorders. Unpublisted doctoral dissertation. University of California, Los Angeles;

Nuechterlein, K.H. (1983). Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. J Abnorm Psychol, 92(1), 4-28.

Nuechterlein, K.H., & Dawson, M.E. (1984). Information processing and attentional functioning in the developmental course of schizophrenic disorders. Schizophr Bull, 10(2), 160-203.

Nuechterlein, K.H. (1986). Annotation: childhood precursors of adult schizophrenia. Journal of Child Psychology and Psychiatry, 27, 133-144.

O'Callaghan, E., Sham, P., Takei, N., Glover, G., & Murray, R.M. (1991). Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic [see comments]. Lancet, 337(8752), 1248-1250.

O'Callaghan, E., Gibson, T., Colohan, H.A., Walshe, D., Buckley, P., Larkin, C., & Waddington, J.L. (1991). Season of birth in schizophrenia. Evidence for confinement of an excess of winter births to patients without a family history of mental disorder [see comments]. Br J Psychiatry, 158, 764-769.

O'Callaghan, E., Larkin, C., Kinsella, A., & Waddington, J.L. (1991). Familial, obstetric, and other clinical correlates of minor physical anomalies in schizophrenia. Am J Psychiatry, 148(4), 479-483.

O'Callaghan, E., Buckley, P., Redmond, O., Stack, J., Ennis, J.T., Larkin, C., & Waddington, J.L. (1992). Abnormalities of cerebral structure in schizophrenia on magnetic resonance imaging: interpretation in relation to the neurodevelopmental hypothesis [see comments]. J R Soc Med, 85(4), 227-231.

O'Callaghan, E., Sham, P.C., Takei, N., Murray, G., Glover, G., Hare, E.H., & Murray, R.M. (1994). The relationship of schizophrenic births to 16 infectious diseases. Br J Psychiatry, 165(3), 353-356.

O'Callaghan, E., Buckley, P., Madigan, C., Redmond, O., Stack, J.P., Kinsella, A., Larkin, C., Ennis, J.T., & Waddington, J.L. (1995). The relationship of minor physical anomalies and other putative indices of developmental disturbance in schizophrenia to abnormalities of cerebral structure on magnetic resonance imaging. Biol Psychiatry, 38(8), 516-524.

O'Callaghan, M.J., Tudehope, D.I., Dugdale, A.E., Mohay, H., Burns, Y., & Cook, F. (1987). Handedness in children with birthweights below 1000 g [letter]. Lancet, 1(8542), 1155

O'Carroll, R., Walker, M., Dunan, J., Murray, C., Blackwood, D., Ebmeier, K.P., & Goodwin, G.M. (1992). Selecting controls for schizophrenia research studies: the use of the National Adult Reading Test (NART) is a measure of premorbid ability. Schizophr Res, 8(2), 137-141.

O'Carroll, R.E. (1987). The inter-rater reliability of the National Adult Reading Test (NART): a pilot study. Br J Clin Psychol, 26 (Pt 3), 229-230.

O'Grady, K.E. (1983). A confirmatory maximum likelihood factor analysis of the WAIS-R. Journal of Consulting and Clinical Psychology, 51(6), 826-831.

Oddy, H.C., & Lobstein, T.J. (1972). Hand and eye dominance in schizophrenia. Br J Psychiatry, 120(556), 331-332.

Office of Population, C.a.S. (1980). Classification of Occupations. London: HMSO.

Offord, D.R., & Cross, L.A. (1971). Adult schizophrenia with scholastic failure or low IQ in childhood. A preliminary report. Arch Gen Psychiatry, 24(5), 431-436.

Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 9(1), 97-113.

Onstad, S., Skre, I., Torgersen, S., & Kringlen, E. (1992). Birthweight and obstetric complications in schizophrenic twins. Acta Psychiatr Scand, 85(1), 70-73.

Orr, K.G., Cannon, M., Gilvarry, C.M., Jones, P.B., & Murray, R.M. (1999). Schizophrenic patients and their first-degree relatives show an excess of mixed-handedness. Schizophr Res, 39(3), 167-176.

Orsini, D.L., & Satz, P. (1986). A syndrome of pathological left-handedness. Correlates of early left hemisphere injury. Arch Neurol, 43(4), 333-337.

Orton, S.T. (1937). Reading, Writing and Speech Problems in Children. London: Chapman and Hall.

Orvaschel, H., Mednick, S., Schulsinger, F., & Rock, D. (1979). The children of psychiatrically disturbed parents: differences as a function of the sex of the sick parent. Arch Gen Psychiatry, 36 (6), 691-695.

Ott, R.L. (1993). An Introduction to Statistical Methods and Data Analysis. (4 ed.). Belmont, Calfornia: Duxbury Press.

Owen, A.M., Roberts, A.C., Polkey, C.E., Sahakian, B.J., & Robbins, T.W. (1991). Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo- hippocampectomy in man. Neuropsychologia, 29(10), 993-1006.

Owen, A.M., Roberts, A.C., Hodges, J.R., Summers, B.A., Polkey, C.E., & Robbins, T.W. (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. Brain, 116 (Pt 5), 1159-1175.

Owen, M.J., Lewis, S.W., & Murray, R.M. (1988). Obstetric complications and schizophrenia: a computed tomographic study. Psychol Med, 18(2), 331-339.

Owens, D.G., Johnstone, E.C., Crow, T.J., Frith, C.D., Jagoe, J.R., & Kreel, L. (1985). Lateral ventricular size in schizophrenia: relationship to the disease process and its clinical manifestations. Psychol Med, 15(1), 27-41.

Ødegård, O. (1932). Emigration and Insanity. Acta Psychiatr Scand, 7, (Suppl. 4), 1-206.

Pantelis, C., Barnes, T.R., Nelson, H.E., & Robbins, T.W. (1991). The nature of dementia in schizophrenia. Psychiatric Bulletin of the Royal College of Psychiatrists, 15(Supplement 4), 63-64.

Park, S., Holzman, P.S., & Goldman-Rakic, P.S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. Arch Gen Psychiatry, 52(10), 821-828.

Parker, K. (1983). Factor analysis of the WAIS-R at nine age levels between 16 and 74 years. J Consult Clin Psychol, 51(2), 302-308.

Parks, R.W., Loewenstein, D.A., Dodrill, K.L., Barker, W.W., Yoshii, F., Chang, J.Y., Emran, A., Apicella, A., Sheramata, W.A., & Duara, R. (1988). Cerebral metabolic effects of a verbal fluency test: a PET scan study. J Clin Exp Neuropsychol, 10(5), 565-575.

Parnas, J., Schulsinger, F., Teasdale, T.W., Schulsinger, H., Feldman, P.M., & Mednick, S.A. (1982). Perinatal complications and clinical outcome within the schizophrenia spectrum. Br J Psychiatry, 140, 416-420.

Parnas, J., Schulsinger, F., Schulsinger, H., Mednick, S.A., & Teasdale, T.W. (1982). Behavioral precursors of schizophrenia spectrum. A prospective study. Arch Gen Psychiatry, 39(6), 658-664.

Parnas, J., Cannon, T.D., Jacobsen, B., Schulsinger, H., Schulsinger, F., & Mednick, S.A. (1993). Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. Results from the Copenhagen High-Risk Study. Arch Gen Psychiatry, 50(9), 707-714.

Paulsen, J.S., Heaton, R.K., Sadek, J.R., Perry, W., Delis, D.C., Braff, D., Kuck, J., Zisook, S., & Jeste, D.V. (1995). The nature of learning and memory impairments in schizophrenia. J Int Neuropsychol Soc, 1(1), 88-99.

Paykel, E.S., Prusoff, B.A., & Uhlenhuth, E.H. (1971). Scaling of life events. Arch Gen Psychiatry, 25(4), 340-347.

Pennington, B.F., Smith, S.D., Kimberling, W.J., Green, P.A., & Haith, M.M. (1987). Left-handedness and immune disorders in familial dyslexics. Arch Neurol, 44(6), 634-639.

Perneger, T.V. (1998). What's wrong with Bonferroni adjustments [see comments]. BMJ, 316(7139), 1236-1238.

Perret, E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. Neuropsychologia, 12(3), 323-330.

Peters, M. (1992). How sensitive are handedness prevalence figures to differences in questionnaire classification procedures? Brain Cogn, 18(2), 208-215.

Petty, R.G. (1999). Structural asymmetries of the human brain and their disturbance in schizophrenia. Schizophr Bull, 25(1), 121-139.

Phillips, J.E., Jacobson, N., & Turner, W.J. (1965). Conceptual thinking in schizophrenics and their relatives. Br J Psychiatry, 111(478), 823-839.

Plake, B.S., Gutkin, T.B., Wise, S.L., & Kroeten, T. (1987). Confirmatory factor analysis of the WAIS--R: Competition of models. Journal of Psychoeducational Assessment, 5(3), 267-272.

Pogue-Geile, M.F. (1990). Siblings of schizophrenic probands: presence of neuropsychological impairments. Schizophr Res, 3, 62

Pogue-Geile, M.F., Garrett, A.H., Brunke, J.T., & Hall, S.K. (1991). Neuropsychological impairments are increased in siblings of schizophrenic parents. Schizophr Res, 4, 390-391.

Pogue-Geile, M.F., Garrett, A.H., Brunke, J.T., Hall, J.K., Crown, J., & Huxley, N. (1992) Susceptibilities to schizophrenia: Neuropsychological studies. Presented at the annual meeting of the Behavior Genetics Association, Boulder, Colorado. (un pub)

Pollin, W., & Stabenau, J.R. (1968). Biological, psychological and historical differences in a series of monozygotic twins discordant for schizophrenia. In D. Rosenthal & S. S.

Kety (Eds.), The Transmission of Schizophrenia. (pp. 317-332). London: Pergamon Press.

Porac, C., Coren, S., Steiger, J.H., & Duncan, P. (1980). Human laterality: a multidimensional approach. Candian Journal of Psychology, 34, 91-96.

Porac, C., Coren, S., & Duncan, P. (1980). Life-span age trends in laterality. J Gerontol, 35(5), 715-721.

Porac, C., & Coren, S. (1981). Lateral Preferences and Human Behaviour. New York: Springer-Verlag.

Portin, P., & Alanen, Y.O. (1997). A critical review of genetic studies of schizophrenia. I. Epidemiological and brain studies. Acta Psychiatr Scand, 95(1), 1-5.

Quitkin, F., Rifkin, A., & Klein, D.F. (1976). Neurologic soft signs in schizophrenia and character disorders. Organicity in schizophrenia with premorbid asociality and emotionally unstable character disorders. Arch Gen Psychiatry, 33(7), 845-853.

Randolph, C., Goldberg, T.E., Gold, J., Daniel, D.G., & Weinberger, D.R. (1990). Left-handedness and ventricle size in schizophrenic patients [letter; comment]. Am J Psychiatry, 147(5), 679-680.

Rantakallio, P., Jones, P., Moring, J., & Von Wendt, L. (1997). Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses: a 28-year follow-up. Int J Epidemiol, 26(4), 837-843.

Raven, J.C., Court, J.H., & Raven, J. (1982). The Mill Hill Vocabulary Scale: 1982 Revision. London: H.K. Lewis.

Razi, K., Greene, K.P., Sakuma, M., Ge, S., Kushner, M., & DeLisi, L.E. (1999). Reduction of the parahippocampal gyrus and the hippocampus in patients with chronic schizophrenia. Br J Psychiatry, 174, 512-519.

Reveley, A.M., Reveley, M.A., & Murray, R.M. (1984). Cerebral ventricular enlargement in non-genetic schizophrenia: a controlled twin study. Br J Psychiatry, 144, 89-93.

Reveley, M.A. (1985). CT scans in schizophrenia. Br J Psychiatry, 146, 367-371.

Rey, A. (1964). L'examen clinique en psychologie. Paris: Presses Universitaires de France.

Ricks, D.F., & Berry, J.C. (1970). Family and symptom patterns that precede schizophrenia. In M. Roff & D. F. Ricks (Eds.), Life History Research in Psychopathology (Vol 1). (pp. 31-50). Minneapolis: University of Minnesota Press.

Risch, N. (1990). Genetic linkage and complex diseases, with special reference to psychiatric disorders. Genet Epidemiol, 7(1), 3-16.

Robbins, T.W. (1990). The case of frontostriatal dysfunction in schizophrenia. Schizophr Bull, 16(3), 391-402.

Roberts, G.W., Colter, N., Lofthouse, R., Bogerts, B., Zech, M., & Crow, T.J. (1986). Gliosis in schizophrenia: a survey. Biol Psychiatry, 21(11), 1043-1050.

Rolf, J.E., Masten, A.S., Cicchetti, D., Nuechterlein, K.H., & Weintraub, S. (1990). Risk and Protective Factors in the Development of Psychopathology. New York: Cambridge University Press.

Rose, R.J., Reed, T., & Bogle, A. (1987). Asymmetry of a-b ridge count and behavioral discordance of monozygotic twins. Behav Genet, 17(2), 125-140.

Rosen, A.J., Lockhart, J.J., Gants, E.S., & Westergaard, C.K. (1991). Maintenance of grip-induced muscle tension: a behavioral marker of schizophrenia. J Abnorm Psychol, 100(4), 583-593.

Rosenthal, D., Wender, P.H., Kety, S.S., Welner, J., & Schulsinger, F. (1971). The adopted-away offspring of schizophrenics. Am J Psychiatry, 128(3), 307-311.

Rosmark, B., Osby, U., Engelbrektson, K., & Nyman, H. (1999). Stability of performance on neuropsychological tests in patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci, 249(6), 299-304.

Ross, G., Lipper, E.G., & Auld, P.A. (1987). Hand preference of four-year-old children: its relationship to premature birth and neurodevelopmental outcome. Dev Med Child Neurol, 29(5), 615-622.

Ross, G., Lipper, E., & Auld, P.A. (1992). Hand preference, prematurity and developmental outcome at school age. Neuropsychologia, 30(5), 483-494.

Rossi, A., Stratta, P., D'Albenzio, L., Tartaro, A., Schiazza, G., di, M., V, Bolino, F., & Casacchia, M. (1990). Reduced temporal lobe areas in schizophrenia: preliminary evidences from a controlled multiplanar magnetic resonance imaging study. Biol Psychiatry, 27(1), 61-68.

Roxborough, H., Muir, W.J., Blackwood, D.H., Walker, M.T., & Blackburn, I.M. (1993). Neuropsychological and P300 abnormalities in schizophrenics and their relatives. Psychol Med, 23(2), 305-314.

Russell, A.J., Munro, J.C., Jones, P.B., Hemsley, D.R., & Murray, R.M. (1997). Schizophrenia and the myth of intellectual decline [see comments]. Am J Psychiatry, 154(5), 635-639.

Rust, J. (1988). The Rust Inventory of Schizotypal Cognitions (RISC). Schizophr Bull, 14(2), 317-322.

Rutschmann, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1977). Sustained attention in children at risk for schizophrenia. Report on a continuous performance test. Arch Gen Psychiatry, 34(5), 571-575.

Rutschmann, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1980). Auditory recognition memory in adolescents at risk for schizophrenia: report on a verbal continuous recognition task. Psychiatry Res, 3(2), 151-161.

Rutschmann, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1986). Sustained attention in children at risk for schizophrenia: findings with two visual continuous performance tests in a new sample. J Abnorm Child Psychol, 14(3), 365-385.

Ryan, J.J., Georgemiller, R.J., Geisser, M.E., & Randall, D.M. (1985). Testetest stability of the WAIS--R in a clinical sample. Journal of Clinical Psychology, 41(4), 552-556.

Saigal, S., Rosenbaum, P., Szatmari, P., & Hoult, L. (1992). Non-right handedness among ELBW and term children at eight years in relation to cognitive function and school performance. Dev Med Child Neurol, 34(5), 425-433.

Saitoh, O., Niwa, S., Hiramatsu, K., Kameyama, T., Rymar, K., & Itoh, K. (1984). Abnormalities in late positive components of event-related potentials may reflect a genetic predisposition to schizophrenia. Biol Psychiatry, 19(3), 293-303.

Sameroff, A.J., Barocas, R., & Seifer, R. (1984). The early development of children born to mentally ill women. In N. F. Watt, E. J. Anthony, & a. et (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 482-514). Cambridge, England UK: Cambridge University Press.

Sanderson, T.L., Best, J.J., Doody, G.A., Owens, D.G., & Johnstone, E.C. (1999). Neuroanatomy of comorbid schizophrenia and learning disability: a controlled study. Lancet, 354(9193), 1867-1871.

Satz, P. (1972). Pathological left-handedness: an explanatory model. Cortex, 8(2), 121-135.

Satz, P. (1973). Left-handedness and early brain insult: an explanation. Neuropsychologia, 11(1), 115-117.

Satz, P. (1980). Incidence of aphasia in left-handers: a test of some hypothetical models of speech organization. In J. Herron (Ed.), Neuropsychology of Left-Handedness. New York: Academic Press.

Satz, P., Orsini, D.L., Saslow, E., & Henry, R. (1985). The pathological left-handedness syndrome. Brain Cogn, 4(1), 27-46.

Satz, P., & Green, M.F. (1999). Atypical handedness in schizophrenia: some methodological and theoretical issues. Schizophr Bull, 25(1), 63-78.

Saunders, D.R. (1960). A factor analysis of the Information and Arithmetic items of the WAIS. Psychological Reprots, 6(367), 383

Sautter, F.J., McDermott, B.E., Cornwell, J., Johnson, J., Borges, A., Wilson, A.F., Vasterling, J.J., & Foundas, A.L. (1995). A preliminary study of the neuropsychological heterogeneity of familial schizophrenia. Schizophr Res, 18(1), 1-7.

Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., & Stafiniak, P. (1991). Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch Gen Psychiatry, 48(7), 618-624.

Saykin, A.J., Shtasel, D.L., Gur, R.E., Kester, D.B., Mozley, L.H., Stafiniak, P., & Gur, R.C. (1994). Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry, 51(2), 124-131.

Schear, J.M., & Sato, S.D. (1989). Effects of visual acuity and visual motor speed and dexterity on cognitive test performance. Archives of Clinical Neuropsychology, 4(1), 25-32.

Scheibel, A.B., & Kovelman, J.A. (1981). Disorientation of the hippocampal pyramidal cells and its process in the schizophrenic patient. Biol Psychiatry, 16, 101-102.

Schneider, W. (1988). Micro Experimental Laboratory: an integrated system for IBM PC compatibles. Behaviour Research Methods, Instruments and Computers, 20, 206-217.

Schreiber, H., Stolz-Born, G., Heinrich, H., Kornhuber, H.H., & Born, J. (1992). Attention, cognition, and motor perseveration in adolescents at genetic risk for schizophrenia and control subjects [published erratum appears in Psychiatry Res 1993 Jul;48(1):91]. Psychiatry Res, 44(2), 125-140.

Schreiber, H., Rothmeier, J., Becker, W., Jurgens, R., Born, J., Stolz-Born, G., Westphal, K.P., & Kornhuber, H.H. (1995). Comparative assessment of saccadic eye movements, psychomotor and cognitive performance in schizophrenics, their first-degree relatives and control subjects. Acta Psychiatr Scand, 91(3), 195-201.

Schwartz, J.M., Aylward, E., Barta, P.E., Tune, L.E., & Pearlson, G.D. (1992). Sylvian fissure size in schizophrenia measured with the magnetic resonance imaging rating protocol of the Consortium to Establish a Registry for Alzheimer's Disease. Am J Psychiatry, 149(9), 1195-1198.

Schwartz, M. (1977). Left-handedness and high-risk pregnancy. Neuropsychologia, 15(2), 341-344.

Schwartz, M. (1988). Handedness, prenatal stress and pregnancy complications. Neuropsychologia, 26(6), 925-929.

Searleman, A., Porac, C., & Coren, S. (1982). The relationship between birth stress and writing hand posture. Brain Cogn, 1(2), 158-164.

Searleman, A., Porac, C., & Coren, S. (1989). Relationship between birth order, birth stress, and lateral preferences: a critical review. Psychol Bull, 105(3), 397-408.

Segalowitz, S.J., Unsal, A., & Dywan, J. (1992). CNV evidence for the distinctiveness of frontal and posterior neural processes in a traumatic brain-injured population. Journal of Clinical and Experimental Neuropsychology, 14(4), 545-565.

Seidman, L.J., Cassens, G., Kremen, W.S., & Pepple J.R. (1992). The Neuropsychology of Schizophrenia. In R. F. White (Ed.), Clinical Syndromes in Adult Neuropsychology: The Practitioners Handbook. (pp. 381-450). Amsterdam: Elsevier.

Selemon, L.D., Rajkowska, G., & Goldman-Rakic, P.S. (1995). Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry, 52(10), 805-818.

Selten, J.P., & Sijben, N. (1994). First admission rates for schizophrenia in immigrants to The Netherlands. The Dutch National Register. Soc Psychiatry Psychiatr Epidemiol, 29(2), 71-77.

Shaffer, D., O'Connor, P.A., Shaffer, S.Q., & Prupis, S. (1983). Neurological soft signs: their origins and significance for behaviour. In M. Rutter (Ed.), Developmental Neuropsychiatry. (pp. 145-163). New York: Guildford Press.

Shallice, T. (1982). Specific impairments in planning. Philosophical Transactions of the Royal Society, 298, 199-209.

Shallice, T., Burgess, P.W., & Frith, C.D. (1991). Can the neuropsychological case-study approach be applied to schizophrenia? Psychol Med, 21(3), 661-673.

Sham, P. (1996). Genetic epidemiology. Br Med Bull, 52(3), 408-433.

Sham, P.C., O'Callaghan, E., Takei, N., Murray, G.K., Hare, E.H., & Murray, R.M. (1992). Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960 [see comments]. Br J Psychiatry, 160, 461-466.

Shan-Ming, Y., Flor-Henry, P., Dayi, C., Tiangi, L., Shuguang, Q., & Zenxiang, M. (1985). Imbalance of hemispheric functions in the major psychoses: a study of handedness in the Peoples Republin of China. Biol Psychiatry, 20, 906-917.

Shedlack, K., Lee, G., Sakuma, M., Xie, S.H., Kushner, M., Pepple, J., Finer, D.L., Hoff, A.L., & DeLisi, L.E. (1997). Language processing and memory in ill and well siblings from multiplex families affected with schizophrenia. Schizophr Res, 25(1), 43-52.

Shimizu, A., Endo, M., Yamaguchi, N., Torii, H., & Isaki, K. (1985). Hand preference in schizophrenics and handedness conversion in their childhood. Acta Psychiatr Scand, 72(3), 259-265.

Shirley, E.A. (1981). A distribution-free method for analysis of covariance based on ranked data. Applied Statistics, 30(2), 158-162.

Shum, D.H., McFarland, K.A., & Bain, J.D. (1990). Construct validity of eight tests of attention: Comparison of normal and closed head injured samples. Clinical Neuropsychologist, 4(2), 151-162.

Shur, E. (1982). Season of birth in high and low genetic risk schizophrenics. Br J Psychiatry, 140, 410-415.

Siegel, C., Waldo, M., Mizner, G., Adler, L.E., & Freedman, R. (1984). Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses. Arch Gen Psychiatry, 41(6), 607-612.

Siegel, S., & Castellan, N.J.Jr. (1988). Nonparametric Statistics for the Behavioural Sciences. (2 ed.). Singapore: McGraw-Hill.

Siever, L.J. (1985). Biological markers in schizotypal personality disorder. Schizophr Bull, 11(4), 564-575.

Silva, D.A., & Satz, P. (1979). Pathological left-handedness: evaluation of a model. Brain Lang, 7(1), 8-16.

Silverstein, M.L., Harrow, M., & Bryson, G.J. (1994). Neuropsychological prognosis and clinical recovery. Psychiatry Res, 52(3), 265-272.

Simons, R.F., MacMillan, F.W., & Ireland, F.B. (1982). Anticipatory pleasure deficit in subjects reporting physical anhedonia: slow cortical evidence. Biol Psychol, 14(3-4), 298-310.

Smart, J.L., Jeffery, C., & Richards, B. (1980). A retrospective study of the relationship between birth history and handedness at six years. Early Hum Dev, 4(1), 79-88.

Smith, D.W. (1988). Recognisable Patterns of Human Malformation. Philadelphia: W.B. Saunders.

Smith, J. (1987). Left-handedness: its association with allergic disease. Neuropsychologia, 25(4), 665-674.

Snow, W.G., Tierney, N.C., & Zorzitto, M.L. (1988). One-year test-retest reliability of selected neuropsychological tests in older adults [Abstract]. Journal of Clinical and Experimental Neuropsychology, 10, 60

Sohlberg, S.C. (1985). Personality and neuropsychological performance of high-risk children. Schizophr Bull, 11(1), 48-60.

Soper, H.V., & Satz, P. (1984). Pathological left-handedness and ambiguous handedness: a new explanatory model. Neuropsychologia, 22(4), 511-515.

Spellacy, F.J., & Spreen, O. (1969). A short form of the token test. Cortex, 5(4), 391-397.

Spreen, O., & Benton, A.L. (1969). Neurosensory Centre Comprehensive Examnatin for Aphasia (NCCEA). Victoria, Australia.: Neuropsychological Labatory, University of Victoria.

Spreen, O., & Benton, A.L. (1977). Neurosensory Centre Comprehensive Examnatin for Aphasia (NCCEA) (revised edn). Victoria, Australia.: Neuropsychological Labatory, University of Victoria.

Spreen, O., & Strauss, E. (1991). A Compendium of Neuropsychological Tests. New York: Oxford University Press.

Spring, B. (1985). Distractibility as a marker of vulnerability to schizophrenia. Psychopharmacol Bull, 21(3), 509-512.

SPSS for Windows, Release 8.0.0 [Computer Software]. (1997). Chicago: Spss Inc.SPSS Inc.

Stainton, A.C. (1985). Stressful Life Events in a Sample at Risk for Psychopathology. The New School for Social Research, New York;

Steg, J.P., & Rapoport, J.L. (1975). Minor physical anomalies in normal, neurotic, learning disabled, and severely disturbed children. J Autism Child Schizophr, 5(4), 299-307.

Steinhauer, S.R., Zubin, J., Condray, R., Shaw, D.B., Peters, J.L., & van Kammen, D.P. (1991). Electrophysiological and behavioural signs of attention disturbance in schizophrenics and their siblings. In C. A. Tamminga & S. C. Schulz (Eds.), Advances in Neuropsychiatry and Psychoparmacology. Vol 1: Schizophrenia Research. New York: Raven Press.

Stephens, W.E., Cunningham, E.S., & Stigler, B.J. (1967). Reading readiness and eye hand preference patterns in first grade children. Except Child, 33(7), 481-488.

Stewart, D.A., Netley, C.T., Bailey, J.D., Haka-Ikse, K., Platt, J., Holland, W., & Cripps, M. (1979). Growth and development of children with X and Y chromosome aneuploidy: a prospective study. Birth Defects Orig Artic Ser, 15(1), 75-114.

Stewart, D.A., Bailey, J.D., Netley, C.T., Rovet, J., Park, E., Cripps, M., & Curtis, J.A. (1982). Growth and development of children with X and Y chromosome aneuploidy from infancy to pubertal age: the Toronto study. Birth Defects Orig Artic Ser, 18(4), 99-154.

Storandt, M. (1976). Speed and coding effects in relation to age and ability level. Developmental Psychology, 12, 177-178.

Strauss, M.E. (1993). Relations of symptoms to cognitive deficits in schizophrenia. Schizophr Bull, 19(2), 215-231.

Suddath, R.L., Casanova, M.F., Goldberg, T.E., Daniel, D.G., Kelsoe, J.R.J., & Weinberger, D.R. (1989). Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. Am J Psychiatry, 146(4), 464-472.

Suddath, R.L., Christison, G.W., Torrey, E.F., Casanova, M.F., & Weinberger, D.R. (1990). Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia [published erratum appears in N Engl J Med 1990 May 31;322(22):1616] [see comments]. N Engl J Med, 322(12), 789-794.

Sweeney, J.A., Haas, G.L., Keilp, J.G., & Long, M. (1991). Evaluation of the stability of neuropsychological functioning after acute episodes of schizophrenia: one-year followup study. Psychiatry Res, 38(1), 63-76.

Sweeney, J.A., Haas, G.L., & Li, S. (1992). Neuropsychological and eye movement abnormalities in first-episode and chronic schizophrenia. Schizophr Bull, 18(2), 283-293.

Takei, N., O'Callaghan, E., Sham, P.C., Glover, G., & Murray, R.M. (1993). Does prenatal influenza divert susceptible females from later affective psychosis to schizophrenia? Acta Psychiatr Scand, 88(5), 328-336.

Takei, N., Sham, P., O'Callaghan, E., Murray, G.K., Glover, G., & Murray, R.M. (1994). Prenatal exposure to influenza and the development of schizophrenia: is the effect confined to females? [see comments]. Am J Psychiatry, 151(1), 117-119.

Takei, N., Van Os, J., & Murray, R.M. (1995). Maternal exposure to influenza and risk of schizophrenia: a 22 year study from The Netherlands. J Psychiatr Res, 29(6), 435-445.

Takei, N., Van Os, J., & Murray, R.M. (1995). Maternal exposure to influenza and risk of schizophrenia: a 22 year study from The Netherlands. J Psychiatr Res, 29(6), 435-445.

Takei, N., Mortensen, P.B., Klaening, U., Murray, R.M., Sham, P.C., O'Callaghan, E., & Munk-Jorgensen, P. (1996). Relationship between in utero exposure to influenza epidemics and risk of schizophrenia in Denmark. Biol Psychiatry, 40(9), 817-824.

Tamlyn, D., McKenna, P.J., Mortimer, A.M., Lund, C.E., Hammond, S., & Baddeley, A.D. (1992). Memory impairment in schizophrenia: its extent, affiliations and neuropsychological character. Psychol Med, 22(1), 101-115.

Taylor, M.A., & Amir, N. (1995). Sinister psychotics. Left-handedness in schizophrenia and affective disorder. J Nerv Ment Dis, 183(1), 3-9.

Taylor, P., Dalton, R., & Fleminger, J.J. (1982). Handedness and schizophrenic symptoms. Br J Med Psychol, 55 (Pt 3), 287-291.

Taylor, P.J., Dalton, R., & Fleminger, J.J. (1980). Handedness in schizophrenia. Br J Psychiatry, 136, 375-383.

Temkin, N.R., Heaton, R.K., Grant, I., & Dikmen, S.S. (1999). Detecting significant change in neuropsychological test performance: a comparison of four models. J Int Neuropsychol Soc, 5(4), 357-369.

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.E., Ronkko, T., Pohjola, J., & Moring, J. (1985). The Finnish adoptive family study of schizophrenia. Yale J Biol Med, 58(3), 227-237.

Tienari, P. (1992). Implications of adoption studies on schizophrenia. Br J Psychiatry Suppl, (18), 52-58.

Tienari, P., Wynne, L.C., Moring, J., Lahti, I., Naarala, M., Sorri, A., Wahlberg, K.E., Saarento, O., Seitamaa, M., & Kaleva, M. (1994). The Finnish adoptive family study of schizophrenia. Implications for family research [see comments]. Br J Psychiatry Suppl, (23), 20-26.

Tienari, P.J., & Wynne, L.C. (1994). Adoption studies of schizophrenia. Ann Med, 26(4), 233-237.

Toomey, R., Faraone, S.V., Seidman, L.J., Kremen, W.S., Pepple, J.R., & Tsuang, M.T. (1998). Association of neuropsychological vulnerability markers in relatives of schizophrenic patients. Schizophr Res, 31(2-3), 89-98.

Torrey, E.F., Torrey, B.B., & Burton-Bradley, B.G. (1974). The epidemiology of schizophrenia in Papua New Guinea. Am J Psychiatry, 131(5), 567-573.

Torrey, E.F., Rawlings, R., & Waldman, I.N. (1988). Schizophrenic births and viral diseases in two states. Schizophr Res, 1(1), 73-77.

Torrey, E.F. (1992). Are we overestimating the genetic contribution to schizophrenia? Schizophr Bull, 18(2), 159-170.

Torrey, E.F., Miller, J., Rawlings, R., & Yolken, R.H. (1997). Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. Schizophr Res, 28(1), 1-38.

Valone, K., Norton, J.P., Goldstein, M.J., & Doane, J.A. (1983). Parental expressed emotion and affective style in an adolescent sample at risk for schizophrenia spectrum disorders. J Abnorm Psychol, 92(4), 399-407.

Ventura, J., Nuechterlein, K.H., Lukoff, D., & Hardesty, J.P. (1989). A prospective study of stressful life events and schizophrenic relapse. J Abnorm Psychol, 98(4), 407-411.

Verdoux, H., Geddes, J.R., Takei, N., Lawrie, S.M., Bovet, P., Eagles, J.M., Heun, R., McCreadie, R.G., McNeil, T.F., O'Callaghan, E., Stober, G., Willinger, M.U., Wright, P., & Murray, R.M. (1997). Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data [see comments]. Am J Psychiatry, 154(9), 1220-1227.

Vollenweider, F.X. (1998). Advances and pathophysiological models of hallucinogenic drug actions in humans: a preamble to schizophrenia research. Pharmacopsychiatry, 31 Suppl 2, 92-103.

Waddington, C.H. (1957). The Strategy of Genes. New York: Macmillan.

Waddington, J.L., O'Callaghan, E., Buckley, P., Larkin, C., Redmond, O., Stack, J., & Ennis, J.T. (1991). The age dependencies of MRI abnormalities in schizophrenia suggest early ventricular enlargement but later prominence of cortical atrophy. Schizophr Res, 5(3), 188-189.

Waddington, J.L. (1993). Neurodynamics of abnormalities in cerebral metabolism and structure in schizophrenia. Schizophr Bull, 19(1), 55-69.

Wahl, O.F. (1976). Handedness in schizophrenia. Percept Mot Skills, 42(3), 944-946.

Wahlberg, K.E., Wynne, L.C., Oja, H., Keskitalo, P., Pykalainen, L., Lahti, I., Moring, J., Naarala, M., Sorri, A., Seitamaa, M., Laksy, K., Kolassa, J., & Tienari, P. (1997). Gene-environment interaction in vulnerability to schizophrenia: findings from the Finnish Adoptive Family Study of Schizophrenia. Am J Psychiatry, 154(3), 355-362.

Waldrop, M.F., Pedersen, F.A., & Bell, R.Q. (1968). Minor physical anomalies and behavior in preschool children. Child Dev, 39(2), 391-400.

Walker, E., & Lewine, R.J. (1990). Prediction of adult-onset schizophrenia from childhood home movies of the patients. Am J Psychiatry, 147(8), 1052-1056.

Walker, E.F., Grimes, K.E., Davis, D.M., & Smith, A.J. (1993). Childhood precursors of schizophrenia: facial expressions of emotion. Am J Psychiatry, 150(11), 1654-1660.

Walker, E.F., Savoie, T., & Davis, D. (1994). Neuromotor precursors of schizophrenia. Schizophr Bull, 20(3), 441-451.

Walker, H.A., & Birch, H.G. (1970). Lateral preference and right-left awareness in schizophrenic children. Journal of Nervous and Mental Disease, (5), 341-351.

Waller, N.G., & Waldman, I.D. (1990). A reexamination of the WAIS--R factor structure. Psychological Assessment, 2(2), 139-144.

Watt, N.F. (1984). In a nutshell: the first two decades of high-risk research in schizophrenia. In N. F. Watt, E. J. Anthony, L. C. Wynne, & J. E. Rolf (Eds.), Children at Risk for Schizophrenia. (pp. 572-595). Cambridge, England UK: Cambridge University Press.

Watt, N.F.E., Anthony, E.J.E., Wynne, L.C.E., & Rolf, J.E.E. (1984). Children at risk for schizophrenia: A longitudinal perspective. Cambridge, England UK: Cambridge University Press.

Wechsler, D. (1955). WAIS Manual. New York: The Psychological Corporation.

Wechsler, D. (1981). WAIS-R manual. New York: Psychological Corporation.

Wechsler, D. (1987). Wechsler Memory Scale-Revised Manual. San Antonio, TX: The Psychological Corporation.

Weinberger, D.R., Torrey, E.F., Neophytides, A.N., & Wyatt, R.J. (1979). Structural abnormalities in the cerebral cortex of chronic schizophrenic patients. Arch Gen Psychiatry, 36(9), 935-939.

Weinberger, D.R., DeLisi, L.E., Perman, G.P., Targum, S., & Wyatt, R.J. (1982). Computed tomography in schizophreniform disorder and other acute psychiatric disorders. Arch Gen Psychiatry, 39(7), 778-783.

Weinberger, D.R., Berman, K.F., & Zec, R.F. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence [see comments]. Arch Gen Psychiatry, 43(2), 114-124.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry, 44(7), 660-669.

Weinberger, D.R., Berman, K.F., & Illowsky, B.P. (1988). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism [see comments]. Arch Gen Psychiatry, 45(7), 609-615.

Weinberger, D.R., Berman, K.F., Suddath, R., & Torrey, E.F. (1992). Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry, 149(7), 890-897.

Wender, P.H., Rosenthal, D., Zahn, T.P., & Kety, S.S. (1971). The psychiatric adjustment of the adopting parents of schizophrenics. Am J Psychiatry, 127(8), 1013-1018.

Westergaard, T., Mortensen, P.B., Pedersen, C.B., Wohlfahrt, J., & Melbye, M. (1999). Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. Arch Gen Psychiatry, 56(11), 993-998.

Whalley, H.C., Kestelman, J.N., Rimmington, J.E., Kelso, A., Abukmeil, S.S., Best, J.J., Johnstone, E.C., & Lawrie, S.M. (1999). Methodological issues in volumetric magnetic resonance imaging of the brain in the Edinburgh High Risk Project. Psychiatry Res, 91(1), 31-44.

Wiens, A.N., McMinn, M.R., & Crossen, J.R. (1988). Rey Auditory-Verbal Learning Test: Development of norms for healthy young adults. Clinical Neuropsychologist, 2(1), 67-87.

Wiersma, D., Giel, R., De Jong, A., & Slooff, C.J. (1983). Social class and schizophrenia in a Dutch cohort. Psychol Med, 13(1), 141-150.

Willner, P. (1997). The dopamine hypothesis of schizophrenia: current status, future prospects. Int Clin Psychopharmacol, 12(6), 297-308.

Wilson, B., Cockburn, J., Baddeley, A., & Hiorns, R. (1989). The development and validation of a test battery for detecting and monitoring everyday memory problems. J Clin Exp Neuropsychol, 11(6), 855-870.

Wilson, B.A., Cockburn, J., & Baddeley, A. (1985). The Rivermead Behavioural Memory Test. Reading: Thames Valley Test Company.

Wing, J.K., Cooper, J.E., & Sartorius, N. (1974). Measurement and Classification of Psychotic Symptoms: An Instruction Manual for the PSE and Catego Programme. London: Cambridge University Press.

Winters, K.C., Stone, A.A., Weintraub, S., & Neale, J.M. (1981). Cognitive and attentional deficits in children vulnerable to psychopathology. J Abnorm Child Psychol, 9(4), 435-453.

Witelson, S.F. (1985). The brain connection: the corpus callosum is larger in left-handers. Science, 229(4714), 665-668.

Witelson, S.F. (1989). Hand and sex differences in the isthmus and genu of the human corpus callosum: a postmortem morphologic study. Brain, 112, 779-835.

Witelson, S.F., & Nowakowski, R.S. (1991). Left out axons make men right: a hypothesis for the origin of handedness and functional asymmetry. Neuropsychologia, 29(4), 327-333.

Witelson, S.F., & Goldsmith, C.H. (1991). The relationship of hand preference to anatomy of the corpus callosum in men. Brain Res, 545(1-2), 175-182.

Woodruff, P.W., McManus, I.C., & David, A.S. (1995). Meta-analysis of corpus callosum size in schizophrenia. J Neurol Neurosurg Psychiatry, 58(4), 457-461.

Woods, B.T., Kinney, D.K., & Yurgelun-Todd, D. (1986). Neurological abnormalities in schizophrenic patients and their families. 1. Comparison of schizophrenic, bipolar and substance abuse patients and normal controls. Arch Gen Psychiatry, 43, 657-663.

Woods, B.T., Yurgelun-Todd, D., Benes, F.M., Frankenburg, F.R., Pope, H.G.J., & McSparren, J. (1990). Progressive ventricular enlargement in schizophrenia: comparison to bipolar affective disorder and correlation with clinical course. Biol Psychiatry, 27(3), 341-352.

Worland, J., & Hesselbrock, V. (1980). The intelligence of children and their parents with schizophrenia and affective illness. J Child Psychol Psychiatry, 21(3), 191-201.

Wynne, L.C., Singer, M.T., & Toohey, M. (1976). Communication of adoptive parents of schizophrenics. In J. Jorstad & E. Ugelstad (Eds.), Schizophrenia 75: Psychotherapy, Family Studies, Research. Oslo: Universitets Forlaget.

Yeo, R.A., Gangestad, S.W., Edgar, C., & Thoma, R. (1999). The evolutionary genetic underpinnings of schizophrenia: the developmental instability model. Schizophr Res, 39(3), 197-206.

Youngjohn, J.R., Larrabee, G.J., & Crook, T.H. (1992). Testetest reliability of computerized, everyday memory measures and traditional memory tests. Clinical Neuropsychologist, 6(3), 276-286.

Zajano, M.J., & Gorman, A. (1986). Stroop interference as a function of percentage of congruent items. Perceptual and Motor Skills, 63(3), 1087-1096.

Zalewski, C., Johnson-Selfridge, M.T., Ohriner, S., Zarrella, K., & Seltzer, J.C. (1998). A review of neuropsychological differences between paranoid and nonparanoid schizophrenia patients. Schizophr Bull, 24(1), 127-145.

Zangwill, O.L. (1960). Cerebral Dominance and its Relation to Psychological Function. Edinburgh: Oliver and Boyd.

Zipursky, R.B., Lim, K.O., Rosenbloom, M., & Pfefferbaum, A. (1988). Differing effects of duration of illness on CT findings in alcoholism and schizophrenia. Psychopharmacol Bull, 24(3), 495-500.

Zornberg, G.L., Buka, S.L., & Tsuang, M.T. (2000). Hypoxic-ischemia-related fetal/neonatal complications and risk of schizophrenia and other nonaffective psychoses: a 19-year longitudinal study. Am J Psychiatry, 157(2), 196-202.

Bibliography of High Risk Studies

The reference list was complied from three main electronic database sources:
PsycINFO,
BIDS EMBASE,
MEDLINE, PUB-MED.

References were incorporated into, and the list generated, by Reference Manager 8.5.

In addition, some pertinent references published in the years pre-dating the coverage of these electronic databases were identified in the bibliography section of relevant books and journal articles, and were manually added to Reference Manager 8.5. This bibliography is no doubt incomplete, particularly concerning book chapters. However the primary motivation for compiling this list was to try to draw together a coherent framework of a broad area of research which could be used as reference resource. The high-risk projects were initially identified through 4 main sources (Asarnow,1988; Garmezy, 1974b; Special Issue of Schizophrenia Bulletin (1987), vol 13, issue 3; Watt et al., 1984). The listing includes all studies identified through these primary sources, some of the references here are not listed in the main PhD Bibliography.

General High-Risk Reviews

Anthony, E.J. (1982). The preventive approach to children at high risk for psychopathology and psychosis. Journal of Children in Contemporary Society, 15, 67-72.

Anthony, E.J. (1987). Children at high risk for psychosis growing up successfully. In E.J. Anthony, B.J. Cohler, et al. (Eds.), The invulnerable child. The Guilford psychiatry series. (pp. 147-184). New York, NY, USA: Guilford Press.

Anthony, E.J. (1987). Risk, vulnerability, and resilience: An overview. In E.J. Anthony, B.J. Cohler, et al. (Eds.), The invulnerable child. The Guilford psychiatry series. (pp. 3-48). New York, NY, USA: Guilford Press.

Asarnow, J.R., & Goldstein, M.J. (1986). Schizophrenia during adolescence and early adulthood: A developmental perspective on risk research. Clinical Psychology Review, 6, 211-235.

Asarnow, J.R. (1988). Children at risk for schizophrenia: converging lines of evidence. Schizophr Bull, 14, 613-631.

Cornblatt, B.A., & Keilp, J.G. (1994). Impaired attention, genetics, and the pathophysiology of schizophrenia [published erratum appears in Schizophr Bull 1994;20(2):248]. Schizophr Bull, 20, 31-46.

Cornblatt, B.A., Dworkin, R.H., Wolf, L.E., & Erlenmeyer-Kimling, L. (1996). Markers, developmental processes, and schizophrenia. In M.F. Lenzenweger, J.J. Haugaard, et al. (Eds.), Frontiers of developmental psychopathology. (pp. 125-147). New York, NY, USA: Oxford University Press.

Cornblatt, B., & Obuchowski, M. (1997). Update of high-risk research: 1987-1997. International Review of Psychiatry, 9, 437-447.

Erlenmeyer-Kimling, L., & Cornblatt, B. (1987). High-risk research in schizophrenia: a summary of what has been learned. J Psychiatr Res, 21, 401-411.

Fish, B. (1975). Biologic antecedents of psychosis in children. Res Publ Assoc Res Nerv Ment Dis, 54, 49-83.

Friedman, D., & Squires-Wheeler, E. (1994). Event-related potentials (ERPs) as indicators of risk for schizophrenia. Schizophr Bull, 20, 63-74.

Garmezy, N., & Streitman, S. (1974). Children at risk: the search for the antecedents of schizophrenia. Part I. Conceptual models and research methods. Schizophr Bull, Spring (8), 14-90.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Glish, M.A., Erlenmeyer-Kimling, L., & Watt, N.F. (1982). Parental assessment of the social and emotional adaptation of children at high risk for schizophrenia. In B.B. Lahey & A.E. Kadzin (Eds.), *Advances in Clinical Child Psychology.* (pp. 181-218).

Goldstein, M.J. (1988). The family and psychopathology. Annu Rev Psychol, 39, 283-299.

Hanson, D.R., Gottesman, I.I., & Heston, L.L. (1990). Long-range schizophrenia forecasting: Many a slip twixt cup and lip. In J.E. Rolf, A.S. Masten, et al. (Eds.), Risk and protective factors in the development of psychopathology. (pp. 424-444). New York, NY, USA: Cambridge University Press.

Kremen, W.S., Seidman, L.J., Pepple, J.R., Lyons, M.J., Tsuang, M.T., & Faraone, S.V. (1994). Neuropsychological risk indicators for schizophrenia: a review of family studies. Schizophr Bull, 20, 103-119.

Lendingham, J.E. (1990). Recent developments in high risk research. In B.B. Lahey, A.E. Kazdin, et al. (Eds.), Advances in clinical child psychology, Vol. 13. Advances in clinical child psychology. (pp. 91-137). New York, NY, USA: Plenum Press.

Lewine, R.R.J., Watt, N.F., & Grubb, T.W. (1984). High-risk-for-schizophrenia research: Sampling bias and its implications. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 557-571). Cambridge, England UK: Cambridge University Press.

Lewine, R.R.J. (1984). Stalking the schizophrenia marker: Evidence for a general vulnerability model of psychopathology. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 545-550). Cambridge, England UK: Cambridge University Press.

Mednick, S.A., & McNeil, T.F. (1968). Current methodology in research on the etiology of schizophrenia: serious difficulties which suggest the use of the high-risk-group method. Psychol Bull, 70, 681-693.

Mednick, S.A., Schulsinger, F., Teasdale, T.W., Schulsinger, H., Venables, P., & Rock, D.R. (1978). Schizophrenia in high-risk children: sex differences in predisposing factors. In Serban G. (Ed.), Cognitive Defects in the Development of Mental Illness. (pp. 169-197). New York: Brunner/ Mazel.

Nuechterlein, K.H., Dawson, M.E., & Green, M.F. (1994). Information-processing abnormalities as neuropsychological vulnerability indicators for schizophrenia. Acta Psychiatr Scand Suppl, 384, 71-79.

Nuechterlein, K.H., Garmezy, N., & Devine, V.T. (1989). Sustained, focused attention under high processing loads: Relevance to vulnerability to schizophrenia. In S.C. Schulz, C.A. Tamminga, et al. (Eds.), Schizophrenia: Scientific progress. (pp. 95-102). New York, NY, USA: Oxford University Press.

Nuechterlein, K.H., Asarnow, R.F., Subotnik, K.L., Fogelson, D.L., Ventura, J., Torquato, R.D., & Dawson, M.E. (1998). Neurocognitive vulnerability factors for schizophrenia: Convergence across genetic risk studies and longitudinal trait-state studies. In M.F. Lenzenweger, R.H. Dworkin, et al. (Eds.), Origins and development of schizophrenia: Advances in experimental psychopathology. (pp. 299-327). Washington, DC, USA: American Psychological Association.

Richters, J.E., & Weintraub, S. (1990). Beyond diathesis: Toward an understanding of high-risk environments. In J.E. Rolf, A.S. Masten, et al. (Eds.), Risk and protective factors in the development of psychopathology. (pp. 67-96). New York, NY, USA: Cambridge University Press.

Tienari, P.J., & Wynne, L.C. (1994). Adoption studies of schizophrenia. Ann Med, 26, 233-237.

Venables, P.H. (1977). The electrodermal psychophysiology of schizophrenics and children at risk for schizophrenia: Controversies and developments. Schizophrenia Bulletin, 3, 28-48.

Venables, P.H. (1993). Electrodermal indices as markers for the development of schizophrenia. In J.C. Roy, W. Boucsein, et al. (Eds.), Progress in electrodermal research. NATO ASI series: Series A: Life sciences, Vol. 249. (pp. 187-205). New York, NY, USA: Plenum Press.

Watt, N.F. (1986). Risk research in schizophrenia and other major psychological disorders. In M. Kessler, S.E. Goldston, et al. (Eds.), A decade of progress in primary prevention. Primary prevention of psychopathology, No. 9. (pp. 115-153). Hanover, NH, USA: University Press of New England.

Watt, N.F., & Saiz, C. (1991). Longitudinal studies of premorbid development of adult schizophrenics. In E.F. Walker et al. (Eds.), Schizophrenia: A life-course developmental perspective. Personality, psychopathology, and psychotherapy series, Vol. 18. (pp. 157-192). San Diego, CA, USA: Academic Press, Inc.

Wynne, L.C. (1984). Communication patterns and family relations of children at risk for schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 551-556). Cambridge, England UK: Cambridge University Press.

St.Louis High-Risk Project

Anthony, B.J. (1978). The development of empathy in high risk children. In E.J. Anthony, C. Koupernik, & C. Chiland (Eds.), The Child in His Family: Vulnerable Children (vol. 6). New York: Wiley.

Anthony, B.J. (1978). Piagetian egocentrism, empathy, and affect discrimination in children at high risk for psychosis. In E.J. Anthony & C. Chiland (Eds.), The Child in His Family: Vulnerable Children (vol. 4). New York: Wiley.

Anthony, E.J. (1969). A clinical evaluation of children with psychotic parents. Am J Psychiatry, 126 (2), 177-184.

Anthony, E.J. (1971). A clinical and experimental study of high-risk children and their schizophrenic parents. In A.R. Kaplan (Ed.), Genetic Factors in Schizophrenia. (pp. 380-406). Springfield, Thomas.

Anthony, E.J. (1975). The influence of a manic-depressive environment on the developing child. In E.J. Anthony & T. Benedek (Eds.), Depression and Human Existence. Boston: Little, Brown.

Anthony, E.J. (1977). Preventative measures for children and adolescents at high risk for psychosis. In G.W. Albee & J.M. Joffee (Eds.), Primary Prevention of Psychopathology. Hanover, N.H.: University Press of New England.

Beck, J.T., & Worland, J. (1983). Rorschach developmental level and its relationship to subsequent psychiatric treatment. J Pers Assess, 47, 238-242.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Janes, C.L., Weeks, D.G., & Worland, J. (1983). School behavior in adolescent children of parents with mental disorder. J Nerv Ment Dis, 171, 234-240.

Janes, C.L., Worland, J., Weeks, D.G., & Konen, P.M. (1984). Interrelationships among possible predictors of schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 160-166). Cambridge, England UK: Cambridge University Press.

Shabad, P., Worland, J., Lander, H., & Dietrich, D. (1979). A retrospective analysis of the TATs of children at risk who subsequently broke down. Child Psychiatry Hum Dev, 10, 49-59.

Worland, J. (1979). Adolescents and adults at genetic risk for psychosis. Int J Rehabil Res, 2, 525-526.

Worland, J. (1979). Rorschach Developmental Level in the offspring of patients with schizophrenia and manic-depressive illness. J Pers Assess, 43, 591-594.

Worland, J., & Hesselbrock, V. (1980). The intelligence of children and their parents with schizophrenia and affective illness. J Child Psychol Psychiatry, 21, 191-201.

Worland, J., Weeks, D.G., Weiner, S.M., & Schechtman, J. (1982). Longitudinal, prospective evaluations of intelligence in children at risk. Schizophr Bull, 8, 135-141.

Worland, J., Weeks, D.G., Janes, C.L., & Strock, B.D. (1984). Intelligence, classroom behavior, and academic achievement in children at high and low risk for psychopathology: a structural equation analysis. J Abnorm Child Psychol, 12, 437-454.

Worland, J., Lander, H., & Hesselbrock, V. (1979). Psychological evaluation of clinical disturbance in children at risk for psychopathology. Journal of Abnormal Psychology, 88, 13-26.

Worland, J., Edenhart-Pepe, R., Weeks, D.G., & Konen, P.M. (1984). Cognitive evaluation of children at risk: IQ, differentiation, and egocentricity. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 148-159). Cambridge, England UK: Cambridge University Press.

Worland, J., Janes, C.L., Anthony, E.J., McGinnis, M., & Cass, L. (1984). St. Louis Risk Research Project: Comprehensive progress report of experimental studies. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 105-147). Cambridge, England UK: Cambridge University Press.

Worland, J., Weeks, D.G., & Janes, C.L. (1987). Predicting mental health in children at risk. In E.J. Anthony, B.J. Cohler, et al. (Eds.), The invulnerable child. The Guilford psychiatry series. (pp. 185-210). New York, NY, USA: Guilford Press.

New York High Risk Project

Amminger, G.P., Pape, S., Rock, D., Roberts, S.A., Ott, S.L., Squires-Wheeler, E., Kestenbaum, C., & Erlenmeyer-Kimling, L. (1999). Relationship between childhood behavioral disturbance and later schizophrenia in the New York High-Risk Project. *Am J Psychiatry, 156,* 525-530.

Cornblatt, B., Obuchowski, M., Roberts, S., Pollack, S., & Erlenmeyer-Kimling, L. (1999). Cognitive and behavioral precursors of schizophrenia. Dev Psychopathol, 11, 487-508.

Cornblatt, B.A., & Erlenmeyer-Kimling, L. (1985). Global attentional deviance as a marker of risk for schizophrenia: specificity and predictive validity. J Abnorm Psychol, 94, 470-486.

Cornblatt, B.A., Lenzenweger, M.F., Dworkin, R.H., & Erlenmeyer-Kimling, L. (1992). Childhood attentional dysfunctions predict social deficits in unaffected adults at risk for schizophrenia. Br J Psychiatry Suppl 18, 59-64.

Cornblatt, B.A., Dworkin, R.H., Wolf, L.E., & Erlenmeyer-Kimling, L. (1996). Markers, developmental processes, and schizophrenia. In M.F. Lenzenweger, J.J. Haugaard, et al. (Eds.), Frontiers of developmental psychopathology. (pp. 125-147). New York, NY, USA: Oxford University Press.

Cornblatt, B., & Erlenmeyer-Kimling, L. (1984). Early attentional predictors of adolescent behavioral disturbances in children at risk for schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 198-211). Cambridge, England UK: Cambridge University Press.

Cornblatt, B., Winters, L., & Erlenmeyer-Kimling, L. (1989). Attentional markers of schizophrenia: Evidence from the New York High-Risk Study. In S.C. Schulz, C.A.

Tamminga, et al. (Eds.), Schizophrenia: Scientific progress. (pp. 83-92). New York, NY, USA: Oxford University Press.

Dworkin, R.H., Green, S.R., Small, N.E., Warner, M.L., Cornblatt, B.A., & Erlenmeyer-Kimling, L. (1990). Positive and negative symptoms and social competence in adolescents at risk for schizophrenia and affective disorder. Am J Psychiatry, 147, 1234-1236.

Dworkin, R.H., Bernstein, G., Kaplansky, L.M., Lipsitz, J.D., Rinaldi, A., Slater, S.L., Cornblatt, B.A., & Erlenmeyer-Kimling, L. (1991). Social competence and positive and negative symptoms: a longitudinal study of children and adolescents at risk for schizophrenia and affective disorder. Am J Psychiatry, 148, 1182-1188.

Dworkin, R.H., Cornblatt, B.A., Friedmann, R., Kaplansky, L.M., Lewis, J.A., Rinaldi, A., Shilliday, C., & Erlenmeyer-Kimling, L. (1993). Childhood precursors of affective vs. social deficits in adolescents at risk for schizophrenia. Schizophr Bull, 19, 563-577.

Dworkin, R.H., Lewis, J.A., Cornblatt, B.A., & Erlenmeyer-Kimling, L. (1994). Social competence deficits in adolescents at risk for schizophrenia. J Nerv Ment Dis, 182, 103-108.

Erlenmeyer-Kimling, L. (1975). A prospective study of children at risk for schizophrenia: Methodological considerations and some preliminary findings. In R.E. Wirt, G. Winoker, & M. Ross (Eds.), Life history research in psychopathology (vol. 4). Minneapolis: University of Minnesota Press.

Erlenmeyer-Kimling, L., & Cornblatt, B. (1978). Attentional measures in a study of children at high-risk for schizophrenia. J Psychiatr Res, 14, 93-98.

Erlenmeyer-Kimling, L., Cornblatt, B., Friedman, D., Marcuse, Y., Rainer, J.D., & Rutschmann, J. (1980). A prospective study of children of schizophrenic parents. Int J Rehabil Res, 3, 90-91.

Erlenmeyer-Kimling, L., Cornblatt, B., Friedman, D., Marcuse, Y., Rutschmann, J., Simmens, S., & Devi, S. (1982). Neurological, electrophysiological, and attentional deviations in children at risk for schizophrenia. In H. A. Nasrallah & F. A. Henn (Eds.), Schizophrenia as a Brain Disease. (pp. 61-98). New York: Oxford University Press.

Erlenmeyer-Kimling, L., Cornblatt, B., & Golden, R.R. (1983). Early indicators of vulnerability to schizophrenia in children at high genetic risk. In S. B. Guze, J. E. Earls, & J. E. Barrell (Eds.), Childhood Psychopathology and Development. (pp. 247-264). New York: Raven Press.

Erlenmeyer-Kimling, L., Marcuse, Y., Cornblatt, B., Friedman, D., Rainer, J.D., & Rutschmann, J. (1984). The New York High-Risk Project. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 169-189). Cambridge, England UK: Cambridge University Press.

Erlenmeyer-Kimling, L., Kestenbaum, C., Bird, H., & Hilldoff, U. (1984). Assessment of the New York High-Risk Project subjects in Sample A who are now clinically deviant. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 227-239). Cambridge, England UK: Cambridge University Press.

Erlenmeyer-Kimling, L., & Cornblatt, B. (1984). Biobehavioral risk factors in children of schizophrenic parents. J Autism Dev Disord, 14, 357-374.

Erlenmeyer-Kimling, L., Friedman, D., Cornblatt, B., & Jacobsen, R. (1985). Electrodermal recovery data on children of schizophrenic parents. Psychiatry Res, 14, 149-161.

Erlenmeyer-Kimling, L., & Cornblatt, B. (1987). The New York High-Risk Project: a followup report. Schizophr Bull, 13, 451-461.

Erlenmeyer-Kimling, L., & Cornblatt, B. (1987). Implications for preventive intervention from prospective research on children at risk for schizophrenia. In J.A. Steinberg, M.M. Silverman, et al. (Eds.), Preventing mental disorders: A research perspective. Department of Health and Human Services publication, No. (ADM)87-1492. (pp. 90-107). Rockville, MD, USA: National Institute of Mental Health.

Erlenmeyer-Kimling, L., Golden, R.R., & Cornblatt, B.A. (1989). A taxometric analysis of cognitive and neuromotor variables in children at risk for schizophrenia. J Abnorm Psychol, 98, 203-208.

Erlenmeyer-Kimling, L., Cornblatt, B.A., Bassett, A.S., Moldin, S.O., Hilldoff-Adamo, U., & Roberts, S. (1990). High-risk children in adolescence and young adulthood: Course of global adjustment. In L.N. Robins, M. Rutter, et al. (Eds.), Straight and devious pathways from childhood to adulthood. (pp. 351-364). Cambridge, England UK: Cambridge University Press.

Erlenmeyer-Kimling, L., Rock, D., Squires-Wheeler, E., Roberts, S., & Yang, J. (1991). Early life precursors of psychiatric outcomes in adulthood in subjects at risk for schizophrenia or affective disorders. Psychiatry Res, 39, 239-256.

Erlenmeyer-Kimling L, Cornblatt BA. (1992). A summary of attentional findings in the New York High-Risk Project. J Psychiatr Res, 26, 405-426.

Erlenmeyer-Kimling, L., Cornblatt, B.A., Rock, D., Roberts, S., Bell, M., & West, A. (1993). The New York High-Risk Project: anhedonia, attentional deviance, and psychopathology. Schizophr Bull, 19, 141-153.

Erlenmeyer-Kimling, L., Squires-Wheeler, E., Adamo, U.H., Bassett, A.S., Cornblatt, B.A., Kestenbaum, C.J., Rock, D., Roberts, S.A., & Gottesman, I.I. (1995). The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow- up. Arch Gen Psychiatry, 52, 857-865.

Erlenmeyer-Kimling, L., Adamo, U.H., Rock, D., Roberts, S.A., Bassett, A.S., Squires-Wheeler, E., Cornblatt, B.A., Endicott, J., Pape, S., & Gottesman, I.I. (1997). The New York High-Risk Project. Prevalence and comorbidity of axis I disorders in offspring of schizophrenic parents at 25-year follow-up. Arch Gen Psychiatry, 54, 1096-1102.

Erlenmeyer-Kimling, L., Roberts, S.A., Rock, D., Adamo, U.H., Shapiro, B.M., & Pape, S. (1998). Prediction from longitudinal assessments of high-risk children. In M.F. Lenzenweger, R.H. Dworkin, et al. (Eds.), Origins and development of schizophrenia: Advances in experimental psychopathology. (pp. 427-445). Washington, DC, USA: American Psychological Association.

Freedman, L.R., Rock, D., Roberts, S.A., Cornblatt, B.A., & Erlenmeyer-Kimling, L. (1998). The New York High-Risk Project: attention, anhedonia and social outcome. *Schizophr Res, 30,* 1-9.

Friedman, D., Vaughan, H.G.J., & Erlenmeyer-Kimling, L. (1982). Cognitive brain potentials in children at risk for schizophrenia: preliminary findings. Schizophr Bull, 8, 514-531.

Friedman, D., Cornblatt, B., Vaughan, H.J., & Erlenmeyer-Kimling, L. (1986). Event-related potentials in children at risk for schizophrenia during two versions of the continuous performance test [published erratum appears in Psychiatry Res 1986 Oct;19(2):175]. Psychiatry Res, 18, 161-177.

Friedman, D., Cornblatt, B., Vaughan, H.J., & Erlenmeyer-Kimling, L. (1988). Auditory event-related potentials in children at risk for schizophrenia: the complete initial sample. Psychiatry Res, 26, 203-221.

Friedman, D., Erlenmeyer-Kimling, L., & Vaughan, H.G.J. (1984). Event-related potential (ERP) methodology in high-risk research. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 190-197). Cambridge, England UK: Cambridge University Press.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Moldin, S.O., Gottesman, I.I., & Erlenmeyer-Kimling, L. (1987). Psychometric validation of psychiatric diagnoses in the New York High- Risk Study [published erratum appears in Psychiatry Res 1988 Mar;23(3):353]. Psychiatry Res, 22, 159-177.

Moldin, S.O., Gottesman, I.I., & Erlenmeyer-Kimling, L. (1987). Searching for the psychometric boundaries of schizophrenia: evidence from the New York High-Risk Study. J Abnorm Psychol, 96, 354-363.

Moldin, S.O., Rice, J.P., Gottesman, I.I., & Erlenmeyer-Kimling, L. (1990). Psychometric deviance in offspring at risk for schizophrenia: II. Resolving heterogeneity through admixture analysis. Psychiatry Res, 32, 311-322.

Moldin, S.O., Gottesman, I.I., Erlenmeyer-Kimling, L., & Cornblatt, B.A. (1990). Psychometric deviance in offspring at risk for schizophrenia: I. Initial delineation of a distinct subgroup. Psychiatry Res, 32, 297-310.

Moldin, S.O., Rice, J.P., Erlenmeyer-Kimling, L., & Squires-Wheeler, E. (1994). Latent structure of DSM-III-R Axis II psychopathology in a normal sample. J Abnorm Psychol, 103, 259-266.

Ott, S.L., Spinelli, S., Rock, D., Roberts, S., Amminger, G.P., & Erlenmeyer-Kimling, L. (1998). The New York High-Risk Project: social and general intelligence in children at risk for schizophrenia. Schizophr Res, 31, 1-11.

Rosenberg, D.R., Sweeney, J.A., Squires-Wheeler, E., Keshavan, M.S., Cornblatt, B.A., & Erlenmeyer-Kimling, L. (1997). Eye-tracking dysfunction in offspring from the New York High-Risk Project: diagnostic specificity and the role of attention. Psychiatry Res, 66, 121-130.

Rutschmann, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1977). Sustained attention in children at risk for schizophrenia. Report on a continuous performance test. Arch Gen Psychiatry, 34, 571-575.

Rutschmann, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1980). Auditory recognition memory in adolescents at risk for schizophrenia: report on a verbal continuous recognition task. Psychiatry Res, 3, 151-161.

Rutschmann, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1986). Sustained attention in children at risk for schizophrenia: findings with two visual continuous performance tests in a new sample. J Abnorm Child Psychol, 14, 365-385.

Squires-Wheeler, E., Skodol, A.E., Bassett, A., & Erlenmeyer-Kimling, L. (1989). DSM-III-R schizotypal personality traits in offspring of schizophrenic disorder, affective disorder, and normal control parents. J Psychiatr Res, 23, 229-239.

Squires-Wheeler, E., Friedman, D., Skodol, A.E., & Erlenmeyer-Kimling, L. (1993). A longitudinal study relating P3 amplitude to schizophrenia spectrum disorders and to global personality functioning. Biol Psychiatry, 33, 774-785.

Watt, N.F., Grubb, T.W., & Erlenmeyer-Kimling, L. (1984). Social, emotional, and intellectual behavior at school among children at high risk for schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 212-226). Cambridge, England UK: Cambridge University Press.

Winters, K.C., Stone, A.A., Weintraub, S., & Neale, J.M. (1981). Cognitive and attentional deficits in children vulnerable to psychopathology. J Abnorm Child Psychol, 9, 435-453.

Minnesota Cross-Sectional Studies

Driscoll, R.M. (1984). Intentional and incidental learning in children vulnerable to psychopathology. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 320-326). Cambridge, England UK: Cambridge University Press.

Garmezy, N. (1973). Competence and adaptation in adult schizophrenic patients and children at risk. In R.S. Dean (Ed.), Schizophrenia: The first ten Dean Award Lectures. (pp. 168-204). New York: M.S.S. Information Corporation.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull,Summer (9), 55-125.

Garmezy, N. (1975). The study of competence in children at risk for severe psychopathology. In E.J. Anthony & C. Koupernik (Eds.), The child and his family: Children at psychiatric risk (vol. 3). New York: Wiley.

Garmezy, N. (1975). The experimental study of children vulnerable to psychopathology. In Anonymous, Child Personality and Psychopathology: Current Topics (vol.2). (pp. 171-216). New York: Wiley Interscience.

Garmezy, N. (1978). Attentional processes in adult schizophrenia and in children at risk. J Psychiatr Res, 14, 3-34.

Garmezy, N., & Devine, V. (1984). Project Competence: The Minnesota studies of children vulnerable to psychopathology. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 289-303). Cambridge, England UK: Cambridge University Press.

Garmezy, N. (1987). Stress, competence, and development: Continuities in the study of schizophrenic adults, children vulnerable to psychopathology, and the search for stress-resistant children. American Journal of Orthopsychiatry, 57, 159-174.

Masten, A.S., Hubbard, J.J., Gest, S.D., Tellegen, A., Garmezy, N., & Ramirez, M. (1999). Competence in the context of adversity: pathways to resilience and maladaptation from childhood to late adolescence. Dev Psychopathol, 11, 143-169.

Nuechterlein, K.H. (1983). Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. J Abnorm Psychol, 92, 4-28.

Nuechterlein, K.H. (1984). Perspectives on future studies of attentional functioning in children at risk for schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 327-332). Cambridge, England UK: Cambridge University Press.

Nuechterlein, K.H. (1984). Sustained attention among children vulnerable to adult schizophrenia and among hyperactive children. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 304-311). Cambridge, England UK: Cambridge University Press.

Nuechterlein, K.H., Garmezy, N., & Devine, V.T. (1989). Sustained, focused attention under high processing loads: Relevance to vulnerability to schizophrenia. In S.C. Schulz, C.A. Tamminga, et al. (Eds.), Schizophrenia: Scientific progress. (pp. 95-102). New York, NY, USA: Oxford University Press.

Nuechterlein, K.H., Phipps-Yonas, S., Driscoll, R., & Garmezy, N. (1990). Vulnerability factors in children at risk: Anomalies in attentional functioning and social behavior. In J.E. Rolf, A.S. Masten, et al. (Eds.), Risk and protective factors in the development of psychopathology. (pp. 445-479). New York, NY, USA: Cambridge University Press.

Phipps-Yonas, S. (1984). Visual and auditory reaction time in children vulnerable to psychopathology. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 312-319). Cambridge, England UK: Cambridge University Press.

Boston; Grunebaum and Gallant

Cohler, B.J., Gallant, D.H., Grunebaum, H.U., Weiss, J.L., & Gamer, E. (1975). Pregnancy and birth complications among mentally ill and well mothers and their children. Soc Biol, 22, 269-278.

Cohler, B.J., Grunebaum, H.U., Weiss, J.L., Gamer, E., & Gallant, D.H. (1977). Disturbance of attention among schizophrenic, depressed and well mothers and their young children. J Child Psychol Psychiatry, 18, 115-135.

Cohler, B.J., & Grunebaum, H. (1982). Children of parents hospitalized for mental illness: II. The evaluation of an intervention program for mentally ill mothers of young children. Journal of Children in Contemporary Society, 15, 57-66.

Gamer, E., Gallant, D., & Grunebaum, H. (1976). Children of psychotic mothers. An evaluation of 1-year-olds on a test of object permanence. Arch Gen Psychiatry, 33, 311-317.

Gamer, E., Gallant, D., Grunebaum, H.U., & Cohler, B.J. (1977). Children of psychotic mothers. Performance of 3-year-old children on tests of attention. Arch Gen Psychiatry, 34, 592-597.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Grunebaum, H., Weiss, J.L., Gallant, D., & Cohler, B.J. (1974). Attention in young children of psychotic mothers. Am J Psychiatry, 131, 887-891.

Grunebaum, H., Weiss, J.L., Cohler, B.J., Hartman, C., & Gallant, D.H. (1975). Mentally Ill Mothers and Their Children. Chicago: University of Chicago Press.

Grunebaum, H., Cohler, B.J., Kauffman, C., & Gallant, D. (1978). Children of depressed and schizophrenic mothers. Child Psychiatry Hum Dev, 8, 219-228.

Herman, J., Mirsky, A.F., Ricks, N.L., & Gallant, D. (1977). Behavioral and electrographic measures of attention in children at risk for schizophrenia. J Abnorm Psychol, 86, 27-33.

Kauffman, C., Grunebaum, H., Cohler, B., & Gamer, E. (1979). Superkids: competent children of psychotic mothers. Am J Psychiatry, 136, 1398-1402.

Swedish High Risk Study

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

McNeil, T.F., & Kaij, L. (1974). Reproduction among female mental patients: obstetric complications and physical size of offspring. Acta Psychiatr Scand, 50, 3-15.

McNeil, T.F., Persson-Blennow, I., & Kaij, L. (1974). Reproduction in female psychiatric patients: severity of mental disturbance near reproduction and rates of obstetric complications. Acta Psychiatr Scand, 50, 23-32.

McNeil, T.F., Kaij, L., & Malmquist-Larsson, A. (1983). Pregnant women with nonorganic psychosis: life situation and experience of pregnancy. *Acta Psychiatr Scand, 68*, 445-457.

McNeil, T.F., Kaij, L., Malmquist-Larsson, A., Naslund, B., Persson-Blennow, I., McNeil, N., & Blennow, G. (1983). Offspring of women with nonorganic psychoses. Development of a longitudinal study of children at high risk. Acta Psychiatr Scand, 68, 234-250.

McNeil, T.F., Kaij, L., & Malmquist-Larsson, A. (1984). Women with nonorganic psychosis: mental disturbance during pregnancy. Acta Psychiatr Scand, 70, 127-139.

McNeil, T.F., Kaij, L., & Malmquist-Larsson, A. (1984). Women with nonorganic psychosis: pregnancy's effect on mental health during pregnancy. Acta Psychiatr Scand, 70, 140-148.

McNeil, T.F., Kaij, L., & Malmquist-Larsson, A. (1984). Women with nonorganic psychosis: factors associated with pregnancy's effect on mental health. Acta Psychiatr Scand, 70, 209-219.

McNeil, T.F., Naslund, B., Persson-Blennow, I., & Kaij, L. (1985). Offspring of women with nonorganic psychosis: mother-infant interaction at three-and-a-half and six months of age. Acta Psychiatr Scand, 71, 551-558.

McNeil, T.F. (1986). A prospective study of postpartum psychoses in a high-risk group. 1. Clinical characteristics of the current postpartum episodes. Acta Psychiatr Scand, 74, 205-216.

McNeil, T.F., & Kaij, L. (1987). Swedish high-risk study: sample characteristics at age 6. Schizophr Bull, 13, 373-381.

McNeil, T.F., Kaij, L., Malmquist-Larsson, A., Naeslund, B., Persson-Blennow, I., McNeil, N., Blennow, G., & Borgenstam, C. (1984). Offspring of women with nonorganic psychoses. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 465-481). Cambridge, England UK: Cambridge University Press.

Naslund, B., Persson-Blennow, I., McNeil, T., Kaij, L., & Malmquist-Larsson, A. (1984). Offspring of women with nonorganic psychosis: fear of strangers during the first year of life. Acta Psychiatr Scand, 69, 435-444.

Naslund, B., Persson-Blennow, I., McNeil, T.F., Kaij, L., & Malmquist-Larsson, A. (1984). Deviations on exploration, attachment, and fear of strangers in high- risk and control infants at one year of age. Am J Orthopsychiatry, 54, 569-577.

Naslund, B., Persson-Blennow, I., McNeil, T., Kaij, L., & Malmquist-Larsson, A. (1984). Offspring of women with nonorganic psychosis: infant attachment to the mother at one year of age. Acta Psychiatr Scand, 69, 231-241.

Naslund, B., Persson-Blennow, I., McNeil, T.F., & Kaij, L. (1985). Offspring of women with nonorganic psychosis: mother-infant interaction at three and six weeks of age. Acta Psychiatr Scand, 71, 441-450.

Persson-Blennow, I., Naslund, B., McNeil, T.F., Kaij, L., & Malmquist-Larsson, A. (1984). Offspring of women with nonorganic psychosis: mother-infant interaction at three days of age. Acta Psychiatr Scand, 70, 149-159.

Persson-Blennow, I., Naslund, B., McNeil, T.F., & Kaij, L. (1986). Offspring of women with nonorganic psychosis: mother-infant interaction at one year of age. Acta Psychiatr Scand, 73, 207-213.

Copenhagen High-Risk Project

Burman, B., Mednick, S.A., Machon, R.A., Parnas, J., & Schulsinger, F. (1987). Children at high risk for schizophrenia: parent and offspring perceptions of family relationships. J Abnorm Psychol, 96, 364-366.

Cannon, T.D., Fuhrmann, M., Mednick, S.A., Machon, R.A., Parnas, J., & Schulsinger, F. (1988). Third ventricle enlargement and reduced electrodermal responsiveness. Psychophysiology, 25, 153-156.

Cannon, T.D., Mednick, S.A., & Parnas, J. (1989). Genetic and perinatal determinants of structural brain deficits in schizophrenia. Arch Gen Psychiatry, 46, 883-889.

Cannon, T.D., Mednick, S.A., & Parnas, J. (1990). Antecedents of predominantly negative- and predominantly positive- symptom schizophrenia in a high-risk population. Arch Gen Psychiatry, 47, 622-632.

Cannon, T.D., Raine, A., Herman, T.M., Mednick, S.A., Schulsinger, F., & Moore, M. (1992). Third ventricle enlargement and lower heart rate levels in a high-risk sample. Psychophysiology, 29, 294-301.

Cannon, T.D., Mednick, S.A., Parnas, J., Schulsinger, F., Praestholm, J., & Vestergaard, A. (1993). Developmental brain abnormalities in the offspring of schizophrenic mothers. I. Contributions of genetic and perinatal factors [see comments]. Arch Gen Psychiatry, 50, 551-564.

Cannon, T.D., & Mednick, S.A. (1993). The schizophrenia high-risk project in Copenhagen: three decades of progress. Acta Psychiatr Scand Suppl, 370, 33-47.

Cannon, T.D., Mednick, S.A., Parnas, J., Schulsinger, F., Praestholm, J., & Vestergaard, A. (1994). Developmental brain abnormalities in the offspring of schizophrenic mothers. II. Structural brain characteristics of schizophrenia and schizotypal personality disorder. Arch Gen Psychiatry, 51, 955-962.

Cannon, T.D., Mednick, S.A., & Parnas, J. (1990). Two pathways to schizophrenia in children at risk. In L.N. Robins, M. Rutter, et al. (Eds.), Straight and devious pathways from childhood to adulthood. (pp. 328-350). Cambridge, England UK: Cambridge University Press.

Carter, J.W., Parnas, J., Cannon, T.D., Schulsinger, F., & Mednick, S.A. (1999). MMPI variables predictive of schizophrenia in the Copenhagen High-Risk Project: a 25-year follow-up. Acta Psychiatr Scand, 99, 432-440.

Cudeck, R., Mednick, S.A., Schulsinger, F., & Schulsinger, H. (1984). A multidimensional approach to the identification of schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 43-70). Cambridge, England UK: Cambridge University Press.

Dykes, K.L., Mednick, S.A., Machon, R.A., Praestholm, J., & Parnas, J. (1992). Adult third ventricle width and infant behavioral arousal in groups at high and low risk for schizophrenia. Schizophr Res, 7, 13-18.

Erel, O., Cannon, T.D., Hollister, J.M., & Mednick, S.A. (1991). Ventricular enlargement and premorbid deficits in school-occupational attainment in a high risk sample. Schizophr Res, 4, 49-52.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Griffith, J.J., Mednick, S.A., Schulsinger, F., & Diderichsen, B. (1980). Verbal associative disturbances in children at high risk for schizophrenia. J Abnorm Psychol, 89, 125-131.

Higgins, J., Gore, R., Gutkind, D., Mednick, S.A., Parnas, J., Schulsinger, F., & Cannon, T.D. (1997). Effects of child-rearing by schizophrenic mothers: a 25-year follow-up. Acta Psychiatr Scand, 96, 402-404.

Hollister, J.M., Mednick, S.A., Brennan, P., & Cannon, T.D. (1994). Impaired autonomic nervous system-habituation in those at genetic risk for schizophrenia. Arch Gen Psychiatry, 51, 552-558.

Itil, T.M., Hsu, W., Saletu, B., & Mednick, S. (1974). Computer EEG and auditory evoked potential investigations in children at high risk for schizophrenia. Am J Psychiatry, 131, 892-900.

John, R.S., Mednick, S.A., & Schulsinger, F. (1982). Teacher reports as a predictor of a schizophrenia and borderline schizophrenia: a Bayesian decision analysis. J Abnorm Psychol, 91, 399-413.

Jorgensen, A., Teasdale, T.W., Parnas, J., Schulsinger, F., Schulsinger, H., & Mednick, S.A. (1987). The Copenhagen high-risk project. The diagnosis of maternal schizophrenia and its relation to offspring diagnosis. Br J Psychiatry, 151, 753-757.

Jorgensen, A., & Parnas, J. (1990). The Copenhagen High-Risk Study. Premorbid and clinical dimensions of maternal schizophrenia. J Nerv Ment Dis, 178, 370-376.

Kirkegaard-Sorensen, L., & Mednick, S.A. (1975). Registered criminality in families with children at high risk for schizophrenia. J Abnorm Psychol, 84, 197-204.

LaFosse, J.M., Mednick, S.A., Praestholm, J., Vestergaard, A., Parnas, J., & Schulsinger, F. (1994). The influence of parental socioeconomic status on CT studies of schizophrenia. Schizophr Res, 11, 285-290.

Machon, R.A., Mednick, S.A., & Schulsinger, F. (1983). The interaction of seasonality, place of birth, genetic risk and subsequent schizophrenia in a high risk sample [published erratum appears in Br J Psychiatry 1987 Jul;151:124]. Br J Psychiatry, 143, 383-388.

Machon, R.A., Mednick, S.A., & Schulsinger, F. (1987). Seasonality, birth complications and schizophrenia in a high risk sample. Br J Psychiatry, 151, 122-124.

Mednick, B.R. (1973). Breakdown in high-risk subjects: familial and early environmental factors. J Abnorm Psychol, 82, 469-475.

Mednick, S.A. (1966). A longitudinal study of children with a high risk for schizophrenia. Ment Hyg, 50, 522-535.

Mednick, S.A., Mura, E., Schulsinger, F., & Mednick, B. (1973). Erratum and further analysis: "perinatal conditions and infant development in children with schizophrenic parents". Soc Biol, 20, 111-112.

Mednick, S.A., & Witkin-Lanoil, G.H. (1977). Intervention in children at high risk for schizophrenia. In G.W. Albee & J.M. Joffee (Eds.), Primary Prevention of Psychopathology. Hanover, N.H.: University Press of New England.

Mednick, S.A., Parnas, J., & Schulsinger, F. (1987). The Copenhagen High-Risk Project, 1962-86. Schizophr Bull, 13, 485-495.

Mednick, S.A. (1970). Breakdown in individuals at high risk for schizophrenia: Possible predispositional perinatal factors. Mental Hygiene, 1, 50-63.

Mednick, S.A., Mura, E., Schulsinger, F., & Mednick, B. (1971). Perinatal conditions and infant development in children with schizophrenic parents. Soc Biol, 18, S103-S113

Mednick, S.A. (1971). Birth defects & schizophrenia. Psychology Today, 4, 49-50-81-81.

Mednick, S.A., Cudeck, R., Griffith, J.J., Talovic, S.A., & Schulsinger, F. (1984). The Danish High-Risk Project: Recent methods and findings. In N.F. Watt, E.J. Anthony, et al.

(Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 21-42). Cambridge, England UK: Cambridge University Press.

Mirdal, G.K., Mednick, S.A., Schulsinger, F., & Fuchs, F. (1974). Perinatal complications in children of schizophrenic mothers. Acta Psychiatr Scand, 50, 553-568.

Olin, S.C., Mednick, S.A., Cannon, T., Jacobsen, B., Parnas, J., Schulsinger, F., & Schulsinger, H. (1998). School teacher ratings predictive of psychiatric outcome 25 years later. Br J Psychiatry Suppl, 172, 7-13.

Olin, S.S., John, R.S., & Mednick, S.A. (1995). Assessing the predictive value of teacher reports in a high risk sample for schizophrenia: a ROC analysis. Schizophr Res, 16, 53-66.

Olin, S.S., Raine, A., Cannon, T.D., Parnas, J., Schulsinger, F., & Mednick, S.A. (1997). Childhood behavior precursors of schizotypal personality disorder. Schizophr Bull, 23, 93-103.

Orvaschel, H., Mednick, S., Schulsinger, F., & Rock, D. (1979). The children of psychiatrically disturbed parents: differences as a function of the sex of the sick parent. Arch Gen Psychiatry, 36, 691-695.

Parnas, J., Schulsinger, F., Teasdale, T.W., Schulsinger, H., Feldman, P.M., & Mednick, S.A. (1982). Perinatal complications and clinical outcome within the schizophrenia spectrum. Br J Psychiatry, 140, 416-420.

Parnas, J., Schulsinger, F., Schulsinger, H., Mednick, S.A., & Teasdale, T.W. (1982). Behavioral precursors of schizophrenia spectrum. A prospective study. Arch Gen Psychiatry, 39, 658-664.

Parnas, J. (1985). Mates of schizophrenic mothers. A study of assortative mating from the American-Danish high risk project. Br J Psychiatry, 146, 490-497.

Parnas, J., Teasdale, T.W., & Schulsinger, H. (1985). Institutional rearing and diagnostic outcome in children of schizophrenic mothers. A prospective high-risk study. Arch Gen Psychiatry, 42, 762-769.

Parnas, J., & Schulsinger, H. (1986). Continuity of formal thought disorder from childhood to adulthood in a high-risk sample. Acta Psychiatr Scand, 74, 246-251.

Parnas, J. (1986). Risk factors in the development of schizophrenia: contributions from a study of children of schizophrenic mothers. Dan Med Bull, 33, 127-133.

Parnas, J., & Teasdale, T.W. (1987). A matched-paired comparison of treated versus untreated schizophrenia spectrum cases. A high-risk population study. Acta Psychiatr Scand, 75, 44-50.

Parnas, J., Jorgensen, A., Teasdale, T.W., Schulsinger, F., & Mednick, S.A. (1988). Temporal course of symptoms and social functioning in relapsing schizophrenics: a 6-year follow-up. Compr Psychiatry, 29, 361-371.

Parnas, J. (1988). Assortative mating in schizophrenia: results from the Copenhagen High-Risk Study. Psychiatry, 51, 58-64.

Parnas, J., & Jorgensen, A. (1989). Pre-morbid psychopathology in schizophrenia spectrum. Br J Psychiatry, 155, 623-627.

Parnas, J., Cannon, T.D., Jacobsen, B., Schulsinger, H., Schulsinger, F., & Mednick, S.A. (1993). Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. Results from the Copenhagen High-Risk Study. Arch Gen Psychiatry, 50, 707-714.

Schulsinger, F., Parnas, J., Petersen, E.T., Schulsinger, H., Teasdale, T.W., Mednick, S.A., Moller, L., & Silverton, L. (1984). Cerebral ventricular size in the offspring of schizophrenic mothers. A preliminary study. Arch Gen Psychiatry, 41, 602-606.

Schulsinger, H. (1976). A ten-year follow-up of children of schizophrenic mothers. Clinical assessment. Acta Psychiatr Scand, 53, 371-386.

Silverton, L., & Mednick, S. (1984). Class drift and schizophrenia. Acta Psychiatr Scand, 70, 304-309.

Silverton, L., Finello, K.M., Mednick, S.A., & Schulsinger, F. (1985). Low birth weight and ventricular enlargement in a high-risk sample. J Abnorm Psychol, 94, 405-409.

Silverton, L., Mednick, S.A., & Harrington, M.E. (1988). Birthweight, schizophrenia and ventricular enlargement in a high-risk sample. Psychiatry, 51, 272-280.

Silverton, L., Mednick, S.A., Schulsinger, F., Parnas, J., & Harrington, M.E. (1988). Genetic risk for schizophrenia, birthweight, and cerebral ventricular enlargement. J Abnorm Psychol, 97, 496-498.

Silverton, L., Harrington, M.E., & Mednick, S.A. (1988). Motor impairment and antisocial behavior in adolescent males at high risk for schizophrenia. J Abnorm Child Psychol, 16, 177-186.

Silverton, L., Finello, K., & Mednick, S. (1983). Children of schizophrenic women: Early factors predictive of schizophrenia. Infant Mental Health Journal, 4, 202-216.

Talovic, S.A., Mednick, S.A., Schulsinger, F., & Falloon, I.R. (1980). Schizophrenia in high-risk subjects: prognostic maternal characteristics. J Abnorm Psychol, 89, 501-504.

Tyrka, A.R., Cannon, T.D., Haslam, N., Mednick, S.A., Schulsinger, F., Schulsinger, H., & Parnas, J. (1995). The latent structure of schizotypy: I. Premorbid indicators of a taxon of individuals at risk for schizophrenia-spectrum disorders. J Abnorm Psychol, 104, 173-183.

Walker, E., Hoppes, E., Emory, E., Mednick, S., & Schulsinger, F. (1981). Environmental factors related to schizophrenia in psychophysiologically labile high-risk males. J Abnorm Psychol, 90, 313-320.

Walker, E.F., Cudeck, R., Mednick, S.A., & Schulsinger, F. (1981). Effects of parental absence and institutionalization on the development of clinical symptoms in high-risk children. Acta Psychiatr Scand, 63, 95-109.

Zorrilla, L.T., Cannon, T.D., Kronenberg, S., Mednick, S.A., Schulsinger, F., Parnas, J., Praestholm, J., & Vestergaard, A. (1997). Structural brain abnormalities in schizophrenia: a family study. Biol Psychiatry, 42, 1080-1086.

The Stonybrook High-Risk Project

Emery, R., Weintraub, S., & Neale, J.M. (1982). Effects of marital discord on the school behavior of children of schizophrenic, affectively disordered, and normal parents. J Abnorm Child Psychol, 10, 215-228.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Harvey, P., Winters, K., Weintraub, S., & Neale, J.M. (1981). Distractibility in children vulnerable to psychopathology. J Abnorm Psychol, 90, 298-304.

Harvey, P.D., Weintraub, S., & Neale, J.M. (1982). Speech competence of children vulnerable to psychopathology. J Abnorm Child Psychol, 10, 373-387.

Harvey, P.D., Weintraub, S., & Neale, J.M. (1985). Span of apprehension deficits in children vulnerable to psychopathology: A failure to replicate. Journal of Abnormal Psychology, 94, 410-413.

Harvey, P.D. (1991). Cognitive and linguistic functions of adolescent children at risk for schizophrenia. In E.F. Walker et al. (Eds.), Schizophrenia: A life-course developmental perspective. Personality, psychopathology, and psychotherapy series, Vol. 18. (pp. 139-156). San Diego, CA, USA: Academic Press, Inc.

Neale, J.M., & Weintraub, S. (1975). Children vulnerable to psychopathology: the Stony Brook high-risk project. J Abnorm Child Psychol, 3, 95-113.

Neale, J.M., Winters, K.C., & Weintraub, S. (1984). Information processing deficits in children at high risk for schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 264-278). Cambridge, England UK: Cambridge University Press.

Neale, J.M., & Harvey, P.D. (1985). Span of apprehension deficits in vulnerable children: Further comments. Journal of Abnormal Psychology, 94, 418-419.

Oltmanns, T.F., Weintraub, S., Stone, A.A., & Neale, J.M. (1978). Cognitive slippage in children vulnerable to schizophrenia. J Abnorm Child Psychol, 6, 237-245.

Weintraub, S., Neale, J.M., & Leibert, D.E. (1975). Teacher ratings of children vulnerable to psychopathology. Am J Orthopsychiatry, 45, 838-845.

Weintraub, S., Prinz, R.J., & Neale, J.M. (1978). Peer evaluations of the competence of children vulnerable to psychopathology. J Abnorm Child Psychol, 6, 461-473.

Weintraub, S., & Neale, J.M. (1984). The Stony Brook High-Risk Project. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 243-263). Cambridge, England UK: Cambridge University Press.

Weintraub, S., & Neale, J.M. (1984). Social behavior of children at risk for schizophrenia. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 279-285). Cambridge, England UK: Cambridge University Press.

Weintraub, S. (1987). Risk factors in schizophrenia: The Stony Brook High-Risk Project. Schizophrenia Bulletin, 13, 439-450.

Winters, K.C., Stone, A.A., Weintraub, S., & Neale, J.M. (1981). Cognitive and attentional deficits in children vulnerable to psychopathology. J Abnorm Child Psychol, 9, 435-453.

Rochester Longitudinal Study

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Sameroff, A.J., & Zax, M. (1973). Perinatal characteristics of the offspring of schizophrenic women. J Nerv Ment Dis, 157, 191-199.

Sameroff, A.J., Seifer, R., & Zax, M. (1982). Early development of children at risk for emotional disorder. Monogr Soc Res Child Dev, 47, 1-82.

Sameroff, A.J., Seifer, R., Barocas, R., Zax, M., & Greenspan, S. (1987). Intelligence quotient scores of 4-year-old children: social- environmental risk factors. Pediatrics, 79, 343-350.

Sameroff, A.J., Seifer, R., Baldwin, A., & Baldwin, C. (1993). Stability of intelligence from preschool to adolescence: the influence of social and family risk factors. Child Dev, 64, 80-97.

Sameroff, A.J., & Seifer, R. (1983). Familial risk and child competence. Child Development, 54, 1254-1268.

Sameroff, A.J., Barocas, R., & Seifer, R. (1984). The early development of children born to mentally ill women. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 482-514). Cambridge, England UK: Cambridge University Press.

Sameroff, A.J., & Seifer, R. (1990). Early contributors to developmental risk. In J.E. Rolf, A.S. Masten, et al. (Eds.), Risk and protective factors in the development of psychopathology. (pp. 52-66). New York, NY, USA: Cambridge University Press.

Seifer, R., Sameroff, A.J., Baldwin, C.P., & Baldwin, A. (1992). Child and family factors that ameliorate risk between 4 and 13 years of age. J Am Acad Child Adolesc Psychiatry, 31, 893-903.

Seifer, R., & Sameroff, A.J. (1987). Multiple determinants of risk and invulnerability. In E.J. Anthony, B.J. Cohler, et al. (Eds.), The invulnerable child. The Guilford psychiatry series. (pp. 51-69). New York, NY, USA: Guilford Press.

Zax, M., Sameroff, A.J., & Babigian, H.M. (1977). Birth outcomes in the offspring of mentally disordered women. Am J Orthopsychiatry, 47, 218-230.

Pittsburg: Schachter and Ragins

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Ragins, N., Schachter, J., Elmer, E., Preisman, R., Bowes, A.E., & Harway, V. (1975). Infants and children at risk for schizophrenia. Environmental and developmental observations. J Am Acad Child Psychiatry, 14, 150-177.

Rubin, J.A., Ragins, N., Schachter, J., & Wimberly, F. (1979). Drawings by schizophrenic and non-schizophrenic mothers and their children. Art Psychotherapy, 6, 163-175.

Schachter, J. (1977). Assessment of mother-infant interaction: Schizophrenic and non-schizophrenic mothers. Merrill Palmer Quarterly, 23, 193-206.

UCLA Family Project

Alkire, A., Goldstein, M., Rodnick, E.H., & Judd, L.L. (1971). Social influence and counterinfluence within families of four types of disturbed adolescents. Journal of Abnormal Psychology, 77, 32-41.

Doane, J.A., Goldstein, M.J., & Rodnick, E.H. (1981). Parental patterns of affective style and the development of schizophrenia spectrum disorders. Fam Process, 20, 337-349.

Doane, J.A., West, K.L., Goldstein, M.J., Rodnick, E.H., & Jones, J.E. (1981). Parental communication deviance and affective style. Predictors of subsequent schizophrenia spectrum disorders in vulnerable adolescents. Arch Gen Psychiatry, 38, 679-685.

Doane, J.A., & Lewis, J.M. (1984). Measurement strategies in family interaction research: A profile approach. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 93-101). Cambridge, England UK: Cambridge University Press.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Goldstein, M.J., Judd, L.L., Rodnick, E.H., Alkire, A., & Gould, E. (1968). A method for studying social influence and coping patterns within families of disturbed adolescents. J Nerv Ment Dis, 147, 233-251.

Goldstein, M.J., Rodnick, E.H., Judd, L.L., & Gould, E. (1970). Galvanic skin reactivity among family groups containing disturbed adolescents. J Abnorm Psychol, 75, 57-67.

Goldstein, M.J., Gould, E., Alkire, A., Rodnick, E.H., & Judd, L.L. (1970). Interpersonal themes in the Thematic Apperception Test stories of families of disturbed adolescents. J Nerv Ment Dis, 150, 354-365.

Goldstein, M.J. (1985). Family factors that antedate the onset of schizophrenia and related disorders: the results of a fifteen year prospective longitudinal study. Acta Psychiatr Scand Suppl, 319, 7-18.

Goldstein, M.J. (1987). The UCLA High-Risk Project. Schizophr Bull, 13, 505-514.

Jones, J.E., Rodnick, E.H., Goldstein, M.J., McPherson, S.R., & West, K.L. (1977). Parental transactional style deviance as a possible indicator of risk for schizophrenia. Arch Gen Psychiatry, 34, 71-74.

Rodnick, E.H., Goldstein, M.J., Lewis, J.M., & Doane, J.A. (1984). Parental communication style, affect, and role as precursors of offspring schizophrenia-spectrum disorders. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 81-92). Cambridge, England UK: Cambridge University Press.

Israeli High Risk Project

Frenkel, E., Kugelmass, S., Nathan, M., & Ingraham, L.J. (1995). Locus of control and mental health in adolescence and adulthood. Schizophr Bull, 21, 219-226.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Ingraham, L.J., Kugelmass, S., Frenkel, E., Nathan, M., & Mirsky, A.F. (1995). Twenty-five-year followup of the Israeli High-Risk Study: current and lifetime psychopathology. Schizophr Bull, 21, 183-192.

Kaffman, M. (1986). The Israeli High-Risk Study: some critical remarks. Schizophr Bull, 12, 151-157.

Kugelmass, S., Faber, N., Ingraham, L.J., Frenkel, E., Nathan, M., Mirsky, A.F., & Ben Shakhar, G. (1995). Reanalysis of SCOR and anxiety measures in the Israeli High-Risk Study. Schizophr Bull, 21, 205-217.

Marcus, J., Hans, S.L., Nagler, S., Auerbach, J.G., Mirsky, A.F., & Aubrey, A. (1987). Review of the NIMH Israeli Kibbutz-City Study and the Jerusalem Infant Development Study. Schizophr Bull, 13, 425-438.

Marcus, J., Hans, S.L., Nagler, S., Auerbach, J.G., Mirsky, A.F., & Aubrey, A. (1989). Review of the NIMH Israeli Kibbutz-City Study and the Jerusalem Infant Development Study. In S. Chess, A. Thomas, et al. (Eds.), Annual progress in child psychiatry and child development, *1988.* (pp. 255-277). New York, NY, USA: Brunner/Mazel, Inc.

Mirsky, A.F., Silberman, E.K., Latz, A., & Nagler, S. (1985). Adult outcomes of high-risk children: differential effects of town and kibbutz rearing. Schizophr Bull, 11, 150-154.

Mirsky, A.F. (1986). The Israeli High-Risk Study: reply to Kaffman. Schizophr Bull, 12, 158-161.

Mirsky, A.F., Kugelmass, S., Ingraham, L.J., Frenkel, E., & Nathan, M. (1995). Overview and summary: twenty-five-year followup of high-risk children. Schizophr Bull, 21, 227-239.

Mirsky, A.F., Ingraham, L.J., & Kugelmass, S. (1995). Neuropsychological assessment of attention and its pathology in the Israeli cohort. Schizophr Bull, 21, 193-204.

Nagler, S., & Mirsky, A.F. (1985). Introduction: the Israeli high-risk study. Schizophr Bull, 11, 19-29.

Nagler, S. (1985). Overall design and methodology of the Israeli high-risk study. Schizophr Bull, 11, 31-37.

Rabin, A.I. (1986). The schizophrenic diathesis and the kibbutz. J Pers Assess, 50, 448-454.

Silberman, E.K., & Mirsky, A.F. (1985). The NIMH-Israeli schizophrenia project: the history of a high-risk study. Schizophr Bull, 11, 146-149.

Silberman, E.K., & Tassone, E.P. (1985). The Israeli high-risk study: statistical overview and discussion. Schizophr Bull, 11, 138-145.

Sohlberg, S.C. (1985). Personality and neuropsychological performance of high-risk children. Schizophr Bull, 11, 48-60.

University of Rochester Child and Family Study

Baldwin, C.P., Baldwin, A.L., Cole, R.E., & Kokes, R.F. (1984). Free Play family interaction and the behavior of the patient in Free Play. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 376-387). Cambridge, England UK: Cambridge University Press.

Cole, R.E., Al-Khayyal, M., Baldwin, A.L., Baldwin, C.P., Fisher, L., & Wynne, L.C. (1984). A cross-setting assessment of family interaction and the prediction of school competence in children at risk. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 388-392). Cambridge, England UK: Cambridge University Press.

Fisher, L., Schwartzman, P., Harder, D., & Kokes, R.F. (1984). A strategy and methodology for assessing school competence in high-risk children. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 355-359). Cambridge, England UK: Cambridge University Press.

Fisher, L., Kokes, R.F., Cole, R.E., Perkins, P.M., & Wynne, L.C. (1987). Competent children at risk: A study of well-functioning offspring of disturbed parents. In E.J. Anthony, B.J. Cohler, et al. (Eds.), The invulnerable child. The Guilford psychiatry series. (pp. 211-228). New York, NY, USA: Guilford Press.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Greenwald, D.F., & Harder, D.W. (1994). Outcome predictors in a longitudinal study of high-risk boys. Journal of Clinical Psychology, 50, 638-643.

Harder, D.W., & Greenwald, D.F. (1992). Parent, family interaction, and child predictors of outcome among sons at psychiatric risk. Journal of Clinical Psychology, 48, 151-164.

Jones, J.E., Wynne, L.C., Al-Khayyal, M., Doane, J.A., Ritzler, B., Singer, M.T., & Fisher, L. (1984). Predicting current school competence of high-risk children with a composite cross-situational measure of parental communication. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 393-413). Cambridge, England UK: Cambridge University Press.

Klein, R.H., & Salzman, L.F. (1978). Censure-praise learning of children at risk. J Nerv Ment Dis, 166, 799-804.

Klein, R.H., & Salzman, L.F. (1981). Response-contingent learning in children at risk. J Nerv Ment Dis, 169, 249-252.

Klein, R.H., & Salzman, L.F. (1984). Response-contingent learning in children at risk. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 371-375). Cambridge, England UK: Cambridge University Press.

Kokes, R.F., Harder, D., Perkins, P., & Strauss, J.S. (1984). Diagnostic, symptomatic, and descriptive characteristics of parents in the University of Rochester Child and Family Study. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 348-354). Cambridge, England UK: Cambridge University Press.

Munson, S., Baldwin, A.L., Yu, P., Baldwin, C.P., & Greenwald, D. (1984). A clinical research approach to the assessment of adaptive function in children at risk. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 360-364). Cambridge, England UK: Cambridge University Press.

Prentky, R.A., Salzman, L.F., & Klein, R.H. (1981). Habituation and conditioning of skin conductance responses in children at risk. Schizophr Bull, 7, 281-291.

Salzman, L.F., & Klein, R.H. (1978). Habituation and conditioning of electrodermal responses in high risk children. Schizophr Bull, 4, 210-222.

Strauss, J.S., Harder, D.W., & Chandler, M. (1979). Egocentrism in children of parents with a history of psychotic disorders. Arch Gen Psychiatry, 36, 191-196.

Wichstrom, L., Holte, A., Husby, R., & Wynne, L.C. (1993). Competence in children at risk for psychopathology predicted from confirmatory and disconfirmatory family communication. Fam Process, 32, 203-220.

Wichstrom, L., Holte, A., & Wynne, L.C. (1993). Disqualifying family communication and anxiety in offspring at risk for psychopathology. Acta Psychiatr Scand, 88, 74-79.

Wichstrom, L., Anderson, A.M., Holte, A., Husby, R., & Wynne, L.C. (1996). Confirmatory and disconfirmatory family communication as predictor of offspring socio-emotional functioning. A 10 to 14 year follow-up of children at risk. Acta Psychiatr Scand, 93, 49-56.

Wichstrom, L., Anderson, A.M., Holte, A., & Wynne, L.C. (1996). Disqualifying family communication and childhood social competence as predictors of offspring's mental health and hospitalization. A 10- to 14-year longitudinal study of children at risk of psychopathology. J Nerv Ment Dis, 184, 581-588.

Wynne, L.C., Cole, R.E., & Perkins, P. (1987). University of Rochester Child and Family Study: risk research in progress. Schizophr Bull, 13, 463-476.

Wynne, L.C. (1984). The University of Rochester Child and Family Study: Overview of research plan. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 335-347). Cambridge, England UK: Cambridge University Press.

Yu, P., Prentky, R., Fisher, L., Baldwin, A.L., Greenwald, D., Munson, S., & Baldwin, C.P. (1984). Child competence as assessed by clincians, parents, teachers, and peers. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 365-370). Cambridge, England UK: Cambridge University Press.

Mauritian Project

Bell, B., Mednick, S.A., Raman, A.C., Schulsinger, F., Sutton-Smith, B., & Venables, P.H. (1975). A longitudinal psychophysiological study of three-year-old Mauritian children: preliminary report. Dev Med Child Neurol, 17, 320-324.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Mednick, S.A., Venables, P.H., Schulsinger, F., Dalais, C., & Van-Dusen, K. (1984). A controlled study of primary prevention: The Mauritius Project. In N.F. Watt, E.J.

Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 71-78). Cambridge, England UK: Cambridge University Press.

Raine, A., & Venables, P.H. (1984). Electrodermal nonresponding, antisocial behavior, and schizoid tendencies in adolescents. Psychophysiology, 21, 424-433.

Raine, A., Venables, P.H., & Williams, M. (1995). High autonomic arousal and electrodermal orienting at age 15 years as protective factors against criminal behavior at age 29 years. Am J Psychiatry, 152, 1595-1600.

Raine, A., Venables, P.H., & Mednick, S.A. (1997). Low resting heart rate at age 3 years predisposes to aggression at age 11 years: evidence from the Mauritius Child Health Project. J Am Acad Child Adolesc Psychiatry, 36, 1457-1464.

Raine, A., Reynolds, C., Venables, P.H., Mednick, S.A., & Farrington, D.P. (1998). Fearlessness, stimulation-seeking, and large body size at age 3 years as early predispositions to childhood aggression at age 11 years [see comments]. Arch Gen Psychiatry, 55, 745-751.

Scarpa, A., Raine, A., Venables, P.H., & Mednick, S.A. (1995). The stability of inhibited/uninhibited temperament from ages 3 to 11 years in Mauritian children. J Abnorm Child Psychol, 23, 607-618.

Scarpa, A., Raine, A., Venables, P.H., & Mednick, S.A. (1997). Heart rate and skin conductance in behaviorally inhibited Mauritian children. J Abnorm Psychol, 106, 182-190.

Schulsinger, F., Mednick, S.A., Venables, P.H., Raman, A.C., & Bell, B. (1975). Early detection and prevention of mental illness: the Mauritius project. A preliminary report. Neuropsychobiology, 1, 166-179.

Venables, P.H. (1989). The Emanuel Miller memorial lecture 1987. Childhood markers for adult disorders. J Child Psychol Psychiatry, 30, 347-364.

Venables, P.H. (1996). Schizotypy and maternal exposure to influenza and to cold temperature: the Mauritius study. J Abnorm Psychol, 105, 53-60.

Venables, P.H. (1997). Maternal exposure to influenza and cold in pregnancy and electrodermal activity in offspring: the Mauritius Study. Psychophysiology, 34, 427-435.

Venables, P.H. (1998). Maternal exposure to influenza in pregnancy and electrodermal activity in offspring: a further study from Mauritius. Psychophysiology, 35, 438-442.

Venables, P.H. (1983). Outcome at age nine of psychophysiological selection at age three for risk of schizophrenia: A Mauritian study. British Journal of Developmental Psychology, 1, 21-30.

McMasters-Waterloo High Risk Project

Asarnow, J.R. (1984). The Waterloo studies of interpersonal competence. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective . (pp. 414-419). Cambridge, England UK: Cambridge University Press.

Asarnow, R.F., Steffy, R.A., MacCrimmon, D.J., & Cleghorn, J.M. (1977). An attentional assessment of foster children at risk for schizophrenia. J Abnorm Psychol, 86, 267-275.

Asarnow, R.F., Steffy, R.A., Cleghorn, J.M., & MacCrimmon, D.J. (1979). The McMaster-Waterloo studies of children at risk for severe psychopathology. In J. Shamie (Ed.), New Directions in Children's Mental Health. New York: Spectrum Press.

Asarnow, R.F., Steffy, R., & Waldman, I. (1985). "Span of apprehension deficits in children vulnerable to psychopathology: A failure to replicate": Comment. Journal of Abnormal Psychology, 94, 414-417.

MacCrimmon, D.J., Cleghorn, J.M., Asarnow, R.F., & Steffy, R.A. (1980). Children at risk for schizophrenia. Clinical and attentional characteristics. Arch Gen Psychiatry, 37, 671-674.

Steffy, R., Asarnow, R.F., Asarnow, J.R., MacCrimmon, D.J., & Cleghorn, J.M. (1984). The McMaster-Waterloo High-Risk Project: Multifaceted strategy for high-risk research. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 401-413). Cambridge, England UK: Cambridge University Press.

New York Infant Development Study

Fish, B. (1957). The detection of schizophrenia in infancy. Journal of Nervous and Mental Disease, 125, 1-24.

Fish, B. (1959). Longitudinal observations of biological deviations in a schizophrenic infant. American Journal of Psychiatry, 116, 25-31.

Fish, B. (1960). Involvement of the central nervous system in infants with schizophrenia. Archives of Neurology, 2, 115-121.

Fish, B., & Alpert, M. (1962). Abnormal states of consciousness and muscle tone in infants born to schizophrenic mothers. Am J Psychiatry, 119, 439-445.

Fish, B., & Alpert, M. (1963). Patterns of neurological development in infants born to schizophrenic mothers. In J. Wortis (Ed.), Recent Advances in Biological Psychiatry. (pp. 37-42). New York: Plenum.

Fish, B., Shapiro, T., Halpern, F., & Wile, R. (1965). The prediction of schizophrenia in infancy: 3. A ten-year followup report of neurological and psychological development. American Journal of Psychiatry, 121, 768-775.

Fish, B., Wile, R., Shapiro, T., & Halpern, F. (1966). The prediction of schizophrenia in infancy. II. A ten-year follow-up report of predictions made at one-month of age. Proc Annu Meet Am Psychopathol Assoc, 54, 335-353.

Fish, B. (1971). Genetic or traumatic developmental deviation? Soc Biol, 18, S117-S119

Fish, B., & Hagin, R. (1972). Visual-motor disorders in infants at risk for schizophrenia. Arch Gen Psychiatry, 27(5), 594-598.

Fish, B. (1975). Biologic antecedents of psychosis in children. Res Publ Assoc Res Nerv Ment Dis, 54, 49-83.

Fish, B. (1976). An approach to prevention in infants at risk for schizophrenia. Developmental deviations from birth to 10 years. J Am Acad Child Psychiatry, 15, 62-82.

Fish, B. (1977). Neurobiologic antecedents of schizophrenia in children. Evidence for an inherited, congenital neurointegrative defect. Arch Gen Psychiatry, 34, 1297-1313.

Fish, B., & Dixon, W.J. (1978). Vestibular hyporeactivity in infants at risk for schizophrenia. Association with critical developmental disorders. Arch Gen Psychiatry, 35, 963-971.

Fish, B. (1982). Attempts at intervention with high-risk children, from infancy on. In M.J. Goldstein (Ed.), Preventive Intervention in Schizophrenia: Are we ready? Washington, D.C.: U.S. Government Printing Office.

Fish, B. (1986). Antecedents of an acute schizophrenic break. J Am Acad Child Psychiatry, 25, 595-600.

Fish, B. (1987). Infant predictors of the longitudinal course of schizophrenic development. Schizophr Bull, 13, 395-409.

Fish, B., Marcus, J., Hans, S.L., Auerbach, J.G., & Perdue, S. (1992). Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem Infant Development Study. Arch Gen Psychiatry, 49, 221-235.

Fish, B., & Hagin, R. (1973). Visual-motor disorders in infants at risk for schizophrenia. Arch Gen Psychiatry, 28(6), 900-904.

Fish, B. (1984). Characteristics and sequelae of the neurointegrative disorder in infants at risk for schizophrenia: 1952-1982. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 423-439). Cambridge, England UK: Cambridge University Press.

Vermont Vulnerable Child Development Project

Fischer, M., Rolf, J.E., Hasazi, J.E., & Cummings, L. (1984). Follow-up of a preschool epidemiological sample: Cross-age continuities and predictions of later adjustment with internalizing and externalizing dimensions of behavior. Child Development, 55, 137-150.

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull, Summer (9), 55-125.

Rolf, J.E. (1972). The social and academic competence of children vulnerable to schizophrenia and other behavior pathologies. J Abnorm Psychol, 80, 225-243.

Rolf, J.E., & Garmezy, N. (1974). The school performance of children vulnerable to behavior pathology. In D.F. Ricks, A. Thomas, & M. Roff (Eds.), Life History Research in Psychopathology (vol. 3). (pp. 87-107). Minneapolis: University of Minnesota Press.

Rolf, J.E. (1976). Peer status and the directionality of symptomatic behavior: prime social competence predictors of outcome for vulnerable children. Am J Orthopsychiatry, 46, 74-88.

Rolf, J.E., & Hasazi, J.E. (1977). Identification of preschool children at risk and some guidelines for primary prevention. In J.M. Joffee & G.W. Albee (Eds.), The Issues: The Primary Prevention of Psychopathology (vol. 1.). (pp. 121-152). Hanover, N.H.: University of New England Press.

Rolf, J.E., Fischer, M., & Hasazi, J.E. (1981). Assessing preventive interventions for multi-risk preschoolers. In M. Goldstein (Ed.), The Prevention of Schizophrenia. (pp. 81-111).

Rolf, J.E., Bevins, S., Hasazi, J.E., Crowther, J., & Johnson, J. (1982). Prospective research with vulnerable children and the risky art of preventive intervention. Prev Hum Serv, 1, 107-122.

Rolf, J.E., Crowther, J., Teri, L., & Bond, L. (1984). Contrasting developmental risks in preschool children of psychiatrically hospitalized parents. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 526-534). Cambridge, England UK: Cambridge University Press.

Jerusalem Infant Development Study

Auerbach, J.G., Hans, S., & Marcus, J. (1993). Neurobehavioral functioning and social behavior of children at risk for schizophrenia [published erratum appears in Isr J Psychiatry Relat Sci 1993;30(2):123]. Isr J Psychiatry Relat Sci, 30, 40-49.

Bernstein, V.J., Jeremy, R.J., & Marcus, J. (1986). Mother-infant interaction in multiproblem families: finding those at risk. J Am Acad Child Psychiatry, 25, 631-640.

Fish, B., Marcus, J., Hans, S.L., Auerbach, J.G., & Perdue, S. (1992). Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem Infant Development Study. Arch Gen Psychiatry, 49, 221-235.

Hans, S.L., Marcus, J., Henson, L., Auerbach, J.G., & Mirsky, A.F. (1992). Interpersonal behavior of children at risk for schizophrenia. Psychiatry, 55, 314-335.

Hans, S.L., Marcus, J., Nuechterlein, K.H., Asarnow, R.F., Styr, B., & Auerbach, J.G. (1999). Neurobehavioral deficits at adolescence in children at risk for schizophrenia: The Jerusalem Infant Development Study. Arch Gen Psychiatry, 56, 741-748.

Hans, S.L., & Marcus, J. (1991). Neurobehavioral development of infants at risk for schizophrenia: A review. In E.F. Walker et al. (Eds.), Schizophrenia: A life-course developmental perspective. Personality, psychopathology, and psychotherapy series, Vol. 18. (pp. 33-57). San Diego, CA, USA: Academic Press, Inc.

Marcus, J., Auerbach, J., Wilkinson, L., & Burack, C.M. (1981). Infants at risk for schizophrenia. The Jerusalem Infant Development Study. Arch Gen Psychiatry, 38, 703-713.

Marcus, J. (1982). Infants at risk for schizophrenia [letter]. Arch Gen Psychiatry, 39, 356-357.

Marcus, J., Hans, S.L., Mednick, S.A., Schulsinger, F., & Michelsen, N. (1985). Neurological dysfunctioning in offspring of schizophrenics in Israel and Denmark. A replication analysis. Arch Gen Psychiatry, 42, 753-761.

Marcus, J., Hans, S.L., Lewow, E., Wilkinson, L., & Burack, C.M. (1985). Neurological findings in high-risk children: childhood assessment and 5- year followup. Schizophr Bull, 11, 85-100.

Marcus, J., Hans, S.L., Byhouwer, B., & Norem, J. (1985). Relationships among neurological functioning, intelligence quotients, and physical anomalies. Schizophr Bull, 11, 101-108.

Marcus, J., Hans, S.L., Nagler, S., Auerbach, J.G., Mirsky, A.F., & Aubrey, A. (1987). Review of the NIMH Israeli Kibbutz-City Study and the Jerusalem Infant Development Study. Schizophr Bull, 13, 425-438.

Marcus, J., Hans, S.L., Auerbach, J.G., & Auerbach, A.G. (1993). Children at risk for schizophrenia: the Jerusalem Infant Development Study. II. Neurobehavioral deficits at school age. Arch Gen Psychiatry, 50, 797-809.

Marcus, J., Auerbach, J., Wilkinson, L., & Burack, C.M. (1984). Infants at risk for schizophrenia: The Jerusalem Infant Development Study. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 440-464). Cambridge, England UK: Cambridge University Press.

Marcus, J., Hans, S.L., Nagler, S., Auerbach, J.G., Mirsky, A.F., & Aubrey, A. (1989). Review of the NIMH Israeli Kibbutz-City Study and the Jerusalem Infant Development Study. In S. Chess, A. Thomas, M. Hertzig. (Eds.), Annual progress in child psychiatry and child development, 1988. (pp. 255-277). New York, NY, USA: Brunner/Mazel, Inc.

Emory University High Risk Project

Goodman, S.H. (1984). Children of disturbed parents: the interface between research and intervention. Am J Community Psychol, 12, 663-687.

Goodman, S.H. (1984). Children of emotionally disturbed mothers: problems and alternatives. Child Today, 13, 6-9.

Goodman, S.H. (1984). Children of disturbed parents: a research-based model for intervention. New Dir Ment Health Serv,(24), 33-51.

Goodman, S.H. (1987). Emory University Project on Children of Disturbed Parents. Schizophr Bull, 13, 411-423.

Goodman, S.H. (1991). Early social and affective development in schizophrenic offspring. In E.F. Walker et al. (Eds.), Schizophrenia: A life-course developmental perspective. Personality, psychopathology, and psychotherapy series, Vol. 18. (pp. 59-91). San Diego, CA, USA: Academic Press, Inc.

Psychosis Proness Study

Chapman, L.J., & Chapman, J.P. (1987). The search for symptoms predictive of schizophrenia. Schizophr Bull, 13, 497-503.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. J Abnorm Psychol, 103, 171-183.

Hanson et al.,: National Institute of Neurological and Communicative Diseases and Stroke Perinatal Project

Garmezy, N. (1974). Children at risk: the search for the antecedents of schizophrenia. Part II: ongoing research programs, issues, and intervention. Schizophr Bull,Summer (9), 55-125.

Hanson, D.R., Gottesman, I.I., & Heston, L.L. (1976). Some possible childhood indicators of adult schizophrenia inferred from children of schizophrenics. Br J Psychiatry, 129, 142-154.

Hanson, D.R., Gottesman, I.I., & Heston, L.L. (1990). Long-range schizophrenia forecasting: Many a slip twixt cup and lip. In J.E. Rolf, A.S. Masten, et al. (Eds.), Risk and protective factors in the development of psychopathology. (pp. 424-444). New York, NY, USA: Cambridge University Press.

Finnish Adoption Study

Tienari, P., Sorri, A., Naarala, M., Lahti, I., Pohjola, J., Bostrom, C., & Wahlberg, K.E. (1983). The Finnish adoptive family study: Adopted-away offspring of schizophrenic mothers. In H. Stierlin, M. Wirshing, & L.C. Wynne (Eds.), Psychosocial Interventions in Schizophrenia: An International View. (pp. 21-34). Berlin/New York: Springer-Verlan.

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.E., Ronkko, T., Pohjola, J., & Moring, J. (1985). The Finnish adoptive family study of schizophrenia. Yale J Biol Med, 58, 227-237.

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.E., Pohjola, J., & Moring, J. (1985). Interaction of genetic and psychosocial factors in schizophrenia. Acta Psychiatr Scand Suppl, 319, 19-30.

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.E., Moring, J., Pohjola, J., & Wynne, L.C. (1987). Genetic and psychosocial factors in schizophrenia: the Finnish Adoptive Family Study. Schizophr Bull, 13, 477-484.

Tienari, P., Lahti, I., Sorri, A., Naarala, M., Moring, J., Wahlberg, K.E., & Wynne, L.C. (1987). The Finnish adoptive family study of schizophrenia. J Psychiatr Res, 21, 437-445.

Tienari, P., Lahti, I., Sorri, A., Naarala, M., Moring, J., & Wahlberg, K.E. (1989). The Finnish adoptive family study of schizophrenia. Possible joint effects of genetic vulnerability and family environment. Br J Psychiatry Suppl 5, 29-32.

Tienari, P. (1991). Interaction between genetic vulnerability and family environment: the Finnish adoptive family study of schizophrenia. Acta Psychiatr Scand, 84, 460-465.

Tienari, P. (1992). Implications of adoption studies on schizophrenia. Br J Psychiatry Suppl 18, 52-58.

Tienari, P., Wynne, L.C., Moring, J., Lahti, I., Naarala, M., Sorri, A., Wahlberg, K.E., Saarento, O., Seitamaa, M., & Kaleva, M. (1994). The Finnish adoptive family study of schizophrenia. Implications for family research [see comments]. Br J Psychiatry Suppl 23, 20-26.

Tienari, P., Lahti, I., Sorri, A., Naarala, M., Wahlberg, K.E., Roenkkoe, T., Moring, J., & Wynne, L.C. (1987). The Finnish adoptive family study of schizophrenia: Possible joint effects of genetic vulnerability and family interaction. In K. Hahlweg, M.J.

Goldstein, et al. (Eds.), Understanding major mental disorder: The contribution of family interaction research. The Family Process Press monograph series. (pp. 33-54). New York, NY, USA: Family Process Press.

Tienari, P., Lahti, I., Sorri, A., Naarala, M., Moring, J., Kaleva, M., Wahlberg, K.E., & Wynne, L.C. (1990). Adopted-away offspring of schizophrenics and controls: The Finnish adoptive family study of schizophrenia. In L.N. Robins, M. Rutter, et al. (Eds.), Straight and devious pathways from childhood to adulthood. (pp. 365-379). Cambridge, England UK: Cambridge University Press.

Wahlberg, K.E., Wynne, L.C., Oja, H., Keskitalo, P., Pykalainen, L., Lahti, I., Moring, J., Naarala, M., Sorri, A., Seitamaa, M., Laksy, K., Kolassa, J., & Tienari, P. (1997). Gene-environment interaction in vulnerability to schizophrenia: findings from the Finnish Adoptive Family Study of Schizophrenia. Am J Psychiatry, 154, 355-362.

Watt: Patterns of Personality Development

Lewine, R.R., Watt, N.F., Prentky, R.A., & Fryer, J.H. (1978). Childhood behaviour in schizophrenia, personality disorder, depression, and neurosis. Br J Psychiatry, 133, 347-357.

Lewine, R.R., Watt, N.F., & Fryer, J.H. (1978). A study of childhood social competence, adult premorbid competence, and psychiatric outcome in three schizophrenic subtypes. J Abnorm Psychol, 87, 294-302.

Prentky, R.A., Lewine, R.R., Watt, N.F., & Fryer, J.H. (1980). A longitudinal study of psychiatric outcome: developmental variables vs. psychiatric symptoms. Schizophr Bull, 6, 139-148.

Watt, N.F., Stolorow, R.D., Lubensky, A.W., & McClelland, D.C. (1970). School adjustment and behavior of children hospitalized for schizophrenia as adults. Am J Orthopsychiatry, 40, 637-657.

Watt, N.F. (1972). Longitudinal changes in the social behavior of children hospitalized for schizophrenia as adults. J Nerv Ment Dis, 155, 42-54.

Watt, N.F., & Lubensky, A.W. (1976). Childhood roots of schizophrenia. J Consult Clin Psychol, 44, 363-375.

Watt, N.F. (1978). Patterns of childhood social development in adult schizophrenics. Arch Gen Psychiatry, 35, 160-165.

Offord: Childhood Antecedents of Adult Schizophrenia; a follow back study

Jones, M.B., & Offord, D.R. (1975). Independent transmission of IQ and schizophrenia. Br J Psychiatry, 126, 185-190.

Offord, D.R., & Cross, L.A. (1971). Adult schizophrenia with scholastic failure or low IQ in childhood. A preliminary report. Arch Gen Psychiatry, 24, 431-436.

Offord, D.R. (1974). School performance of adult schizophrenics, their siblings and age mates. Br J Psychiatry, 125, 12-19.

Pollock: Schizophrenics and non-schizophrenics and their siblings; a retrospective study

Pollack, M., Woerner, M.G., Goodman, W., & Greenberg, I.M. (1966). Childhood development patterns of hospitalized adult schizophrenic and nonschizophrenic patients and their siblings. Am J Orthopsychiatry, 36, 510-517.

Pollack, M., Jaffe, R., Woerner, M.G., & Klein, D.F. (1969). Fourteen and six per second positive spikes in psychiatric patients and their sibs. Electroencephalogr Clin Neurophysiol, 27, 669-670.

Pollack, M., Woerner, M.G., Goldberg, P., & Klein, D.F. (1969). Siblings of schizophrenic and nonschizophrenic psychiatric patients. Psychopathology and gender concordance. Arch Gen Psychiatry, 20, 652-658.

Reider and Nicol: National Institute of Neurological and Communicative Disease and Stroke Perinatal Project

Rieder, R.O., Rosenthal, D., Wender, P., & Blumenthal, H. (1975). The offspring of schizophrenics. Fetal and neonatal deaths. Arch Gen Psychiatry, 32, 200-211.

Rieder, R.O., Broman, S.H., & Rosenthal, D. (1977). The offspring of schizophrenics. II. Perinatal factors and IQ. Arch Gen Psychiatry, 34, 789-799.

Rieder, R.O., & Nichols, P.L. (1979). Offspring of schizophrenics. III. Hyperactivity and neurological soft signs. Arch Gen Psychiatry, 36, 665-674.

Wrede: Pregnancy and Delivery Complications in Finnish Children with Schizophrenic Mothers

Wrede, G., Mednick, S.A., Huttunen, M.O., & Nilsson, C.G. (1980). Pregnancy and delivery complications in the births of an unselected series of Finnish children with schizophrenic mothers. Acta Psychiatr Scand, 62, 369-381.

Wrede, G., Mednick, S.A., Huttunen, M.O., & Nilsson, C.G. (1984). Pregnancy and delivery complications in the births of an unselected series of Finnish children with schizophrenic mothers: II. In N.F. Watt, E.J. Anthony, et al. (Eds.), Children at risk for schizophrenia: A longitudinal perspective. (pp. 515-525). Cambridge, England UK: Cambridge University Press.

Appendices

Appendix 1 Appendix to Chapter 2, section 2.6.14

Table 2.6.14.1. School difficulties

	High Risk seen n=79 (1 missing)	High Risk not seen n=27 (2 missing)	Control seen n=22	Control not seen n=11
Never in residential school	79 (100)	25 (92.6)	22 (100)	11 (100)
In residential school		2 (7.4)		
TIME OFF SCHOOL				
No time off school	62 (78.5)	22 (81.5)	17 (77.3)	11 (100)
Self reported mild truancy	4 (5.1)		2 (9.1)	
Self reported extreme truancy	8 (10.1)	4 (14.8)		
Time off school for other reason (e.g. medical)	5 (6.3)	1 (3.4)	3 (13.6)	

Table 2.6.14.2. Social work involvement

	High Risk seen n=79 (1 missing)	High Risk not seen n=27 (2 missing)	Control seen n=22	Control not seen n=11
SOCIAL WORK INPUT				
None	59 (74.7)	19 (70.4)	22 (100)	10 (90.9)
Fostered	4 (5.1)	1 (3.7)		1 (9.1)
Other family involvement	12 (15.2)	4 (14.8)		
In Care	3 (3.8)	1 (3.7)		
Social work input due to childrens panel attendence	1 (1.3)	2 (7.4)		
APPEARANCE BEFORE CHILDRENS PANEL				
No	73 (92.4)	22 (81.5)	22 (100)	11 (100)
Due to truancy	3 (3.8)	1 (3.7)		
Due to other behavioural problems	1 (1.3)	2 (7.4)		
Due to family problems	1 (1.3)			
Other	1 (1.3)	2 (7.4)		

Table 2.6.14.3. Psychological difficulties

	High Risk seen n=80	High Risk not seen n=27 (2 missing)	Control seen n=22	Control not seen n=11
No reported difficulties	53 (66.3)	19 (70.4)	21 (95.5)	9 (81.8)
Saw GP/Counsellor for Depression	3 (3.8)	1 (3.7)		1 (9.1)
Saw GP/Counsellor other psychological problem	6 (7.5)	4 (14.8)		
YPU/psychiatric contact	7 (8.8)	2 (7.4)	1 (4.5)	
Other problem	5 (6.3)			
Attended Dept. of Child and Family Therapy	3 (3.8)	1 (3.7)		1 (9.1)
Depression/Anxiety requiring medication	3 (3.8)			

Table 2.6.14.4 Forensic history

	High Risk seen n=79 (1 missing)	High Risk not seen n=27 (2 missing)	Control seen n=22	Control not seen n=11
None	64 (80.1)	20 (74.1)	19 (86.4)	9 (81.8)
Warned not charged	13 (16.3)	2 (7.4)	2 (9.1)	2 (18.2)
Charged/ convicted	3 (3.8)	5 (18.5)	1 (4.5)	

Table 2.6.14.5. Educational qualifications

	High Risk seen n=79 (1 missing)	High Risk not seen n=27 (2 missing)	Control seen n=22	Control not seen n=11
Left school before exams	5 (6.3)	4 (14.8)	1 (4.5)	
Sat leaving exam (O / Standard Grades/ Highers/A Levels)	26 (32.9)	9 (33.3)	4 (18.2)	4 (36.4)
Cert. /diploma entry	16 (20.2)	6 (22.2)	3 (13.6)	2 (18.2)
Degree/post grad entry	21 (26.6)	1 (3.7)	12 (54.5)	3 (27.3)
Vocational Training	6 (7.6)	4 (14.8)	1 (4.5)	
Still at school	5 (6.3)	3 (11.1)	1 (4.5)	2 (18.2)

Table 2.6.14.6. Family history

	High Risk seen n=80	High Risk not seen n=29	Control seen n=22	Control not seen n=11
No family history (Control group)			22 (100)	11 (100)
Two or more 2nd degree	23 (28.8)	10 (34.5)		
One 1st degree (and second degree)	50 (62.5)	12 (41.4)		
Two or more 1st degree	7 (8.8)	7 (24.1)		

Table 2.6.14.7. Learning difficulties (reading or writing problems)

	High Risk seen n=79 (1 missing)	High Risk not seen n=27 (2 missing)	Control seen n=22	Control not seen n=11
Reading/writing problems				
No learning difficulties	69 (87.3)	23 (85.2)	19 (86.4)	11 (100)
Remedial classes	5 (6.3)	1 (3.7)		
Self reported difficulties but no intervention	4 (5.1)	2 (7.4)	3 (13.6)	
Diagnosed dyslexia	1 (1.3)	1 (3.7)		
Speech problems	**High Risk seen n=79 (1 missing)**	**High Risk not seen n=27 (2 missing)**	**Control seen n=22**	**Control not seen n=11**
No speech problems	66 (83.5)	24 (88.9)	19 (86.4)	11 (100)
Self reported problems no speech therapy input	5 (6.3)		1 (4.5)	
Speech Therapy input	8 (10.1)	3 (11.1)	2 (9.1)	

Table 2.6.14.8. PSE symptoms

	High Risk seen n=78 (2 missing)	High Risk not seen n=27 (2 missing)	Control seen n=22	Control not seen n=11
PSE at VISIT ONE				
No symptoms	45 (57.7)	12 (44.4)	10 (72.7)	9 (81.8)
Score of 1	18 (23.1)	4 (14.8)	2 (9.1)	2 (18.2)
Score of 2	6 (7.7)	5 (18.5)	1 (4.5)	
Score of 3	9 (11.5)	6 (22.2)	3 (13.6)	
PSE SYMPTOMS EVER				
No symptoms	36 (45.0)	12 (41.4)	15 (68.2)	9 (81.8)
Score of 1	21 (26.3)	4 (14.8)	3 (13.6)	2(18.2)
Score of 2	9 (11.3)	5 (18.5)	1 (4.5)	
Score of 3	8 (10.0)	6 (22.2)	3 (13.6)	
Score of 4	6 (7.5)			

Table 2.6.14.9. Social class of origin

	High Risk seen n=80	High Risk not seen n=28 (2 missing)	Control seen n=22	Control not seen n=11
Social Class of Origin				
1 and II	22 (27.5)	4 (13.8)	10 (45.5)	1 (9.1)
III and IV	42 (52.5)	14 (48.3)	9 (40.9)	5 (45.5)
V and VI	13 (16.3)	9 (31.0)	3 (13.6)	3 (27.3)
Unclassifiable	3 (3.8)	2 (6.9)		2 (18.2)

Table 2.6.14.10. Drug usage

	High Risk seen	High Risk not seen	Control seen	Control not seen
Current cannabis usage	n=78(2 missing)	n=27(2 missing)	n=22	n=11
None	54 (69.2)	19 (70.4)	16 (45.5)	10 (90.9)
Occasional	19 (24.4)	3 (11.1)	4 (18.2)	1 (9.1)
Frequent/Severe	5 (6.4)	5 (18.5)	2 (9.1)	
Past cannabis usage	n=77(3 missing)	n=27(2 missing)	n=22	n=11
None	35 (45.5)	13 (48.1)	10 (45.5)	3 (27.3)
Occasional	34 (44.2)	10 (37.0)	11 (50.0)	8 (72.7)
Frequent/Severe	8 (10.4)	4 (14.8)	1 (4.5)	
Current other drug usage	n=78(2 missing)	n=28(1 missing)	n=22	n=11
None	68 (87.2)	21 (75.0)	18 (81.8)	10 (90.9)
Occasional	9 (11.5)	4 (14.3)	3 (13.6)	1 (9.1)
Frequent/Severe	1 (1.3)	3 (10.7)	1 (4.5)	
Past other drug usage				
None	50 (64.1)	16 (57.1)	13 (59.1)	7 (63.6)
Occasional	22 (28.2)	9 (32.1)	7 (31.8)	3 (27.3)
Frequent/Severe	6 (7.7)	3 (10.7)	2 (9.1)	1 (9.1)
Alcohol usage, past and present	n=78(2 missing)	n=26(3 missing)	n=22	n=11
None	15 (19.2)	4 (15.4)	3 (13.6)	
Occasional	48 (61.5)	17 (65.4)	12 (54.5)	9 (81.8)
Frequent/Severe	15 (19.2)	5 (19.2)	7 (31.8)	2 (18.2)

Appendix 2. Appendix to Chapter four

Table 4.3. Exploratory data analysis, means (standard deviations), and medians (25th and 75th percentiles of the distribution)

Variables	CONTROLS			HIGH RISK			PATIENTS		
	Mean (sd)	N	Median (25th, 75th P)	Mean (sd)	N	Median (25th, 75th P	Mean (sd)	N	Median(25th P, 75th P)
Token Test A	7 (0)	34		7 (0)	150		7 (0)	25	
Token Test B	8 (0)	34		8 (0)	150		7.96 (0.2)	25	8 (8, 8)
Token Test C	12 (0)	34		11.95 (0.24)	150	12 (12, 12)	11.96 (0.2)	25	12 (12, 12)
Token Test D	16 (0)	34		15.95 (0.35)	150	16 (16, 16)	15.92 (0.28)	25	16 (16, 16)
Token Test E	24 (0)	34		23.91 (0.35)	150	24 (24, 24)	23.68 (0.80)	25	24 (24, 24)
Token Test F	95.18 (1.94)	34	96 (95, 96)	94.83 (1.99)	150	96 (94, 96)	92.64 (3.76)	25	94 (90, 96)
Token Test Total	162.18 (1.94)	34	163 (162,163)	161.66 (2.05)	150	163 (161, 163)	159.24 (4.05)	25	160 (157.5, 162.5)
Nart FSIQ	105.23 (8.36)	34	106 (100, 112)	98.36 (9.87)	152	99 (92, 104.5)	96.56 (9.35)	25	96 (89.5, 104)
Information	8.56 (2.64)	34	9 (6,10)	7.57 (2.54)	157	7 (5, 10)	7.59 (2.80)	27	7 (5, 10)
Digit Span	10.32(2.47)	34	10 (8,12)	9.94 (2.55)	157	10 (8, 12)	8.37 (2.53)	27	8 (6, 10)
Vocabulary	9.38 (1.87)	34	10 (8, 11)	8.38 (2.13)	157	8 (7, 10)	7.56 (2.31)	27	8 (6, 9)
Arithmetic	10.21 (3.01)	34	10.5 (8, 12.25)	9.34 (2.43)	157	9 (7, 11)	7.96 (2.87)	27	7 (6, 10)
Comprehension	10.21 (2.10)	34	10 (9, 11.25)	8.99 (2.29)	157	9 (7, 10)	7.74 (2.43)	27	7 (6, 10)
Similarities	10.53 (2.52)	34	10 (9, 12.25)	9.36 (2.21)	157	10 (8, 11)	8.0 (2.77)	27	8 (6, 10)
Picture Completion	9.71(2.35)	34	9.5 (8,11)	9.13 (2.48)	157	9 (7, 11)	8.07 (1.98)	27	9 (6, 10)
Picture Arrangement	10.41 (2.74)	34	11 (8, 12)	10.12 (2.53)	157	11 (8, 12)	8.44 (2.91)	27	8 (6, 10)
Block Design	13.12 (3.16)	34	13.5 (11, 15.25)	10.97 (2.82)	157	11 (9, 13)	10.44 (3.52)	27	10 (7, 12)
Object Assembly	10.56 (2.75)	34	10 (9, 12)	9.48 (2.52)	157	10 (7, 11)	8.30 (2.60)	27	9 (6, 10)
Digit Symbol	11.26 (2.71)	34	11 (10, 13.25)	9.90 (2.69)	157	10 (8, 12)	7.89 (2.59)	27	7 (6, 10)
Verbal I.Q.	102.85 (12.61)	34	104 (96.5, 112.25)	96.62 (11.58)	157	95 (89, 104)	90.15 (14.18)	27	89 (80, 99)
Performance I.Q.	107.68 (15.88)	34	108 (96, 118)	99.81 (14.25)	157	98 (89, 1095)	90.48 (13.52)	27	90 (82, 97)
Full Scale I.Q.	105.47 (14.13)	34	105.5 (99, 115.25)	97.77 (12.84)	157	97 (88, 106)	89.52 (13.97)	27	87 (80, 98)
Verbal Fluency 'F'	13.73 (3.99)	34	14 (10.75, 16)	12.81 (4.76)	151	12 (10, 15)	9.74 (3.0)	23	10 (7, 12)
Verbal Fluency 'A'	11.44 (3.55)	34	12 (9, 14)	10.71 (4.12)	150	10 (8, 13)	7.35 (3.16)	23	6 (5, 10)
Verbal Fluency 'S'	153.35 (4.32)	34	15 (12.75, 18)	14.40 (4.66)	151	14 (12, 17)	11 (3.67)	23	11 (10, 16)
Animals	17.97 (6.31)	33	18 (13.5, 21.5)	15.57 (4.58)	149	15 (13, 18)	12.26 (3.84)	23	11 (10, 16)
Stroop	21.31 (5.087	32	20.85 (17.85, 24.95)	23.61 (5.54)	146	22.9 (19.7, 26.67)	25.90 (5.01)	24	26.45 (22.55, 29.17)
Spot The Word	11.03 (2.25)	32	11 (9, 12.75)	9.46 (2.44)	147	9 (8, 11)	9.46 (2.91)	26	9 (7.75, 12)

Variables	CONTROLS			HIGH RISK			PATIENTS		
	Mean (sd)	N	Median (25th, 75th P)	Mean (sd)	N	Median (25th, 75th P	Mean (sd)	N	Median(25th P, 75th P)
Speed of comprehension	12.37 (3.17)	32	12 (10.25, 15)	10.93 (3.27)	147	11 (9, 13)	8.78 (3.32)	27	8 (6, 12)
Visual Reproductions 1	37.59 (2.80)	32	28 (36, 40)	35.24 (3.92)	144	36 (33, 38)	33.57 (5.38)	28	34 (32.25, 37)
Visual Reproductions 2	35.5 (4.42)	32	36 (33, 39)	32.77 (5.49)	144	34 (30, 37)	29.39 (7.08)	28	31 (27, 35)
Ravlt I	7.29 (1.93)	34	7 (6, 8)	6.34 (1.85)	149	6 (5, 8)	5.71 (2.27)	28	6 (4.25, 6.75)
Ravlt II	9.97 (2.29)	34	10 (8, 12)	9.42 (2.30)	149	9 (8, 11)	8.32 (2.18)	28	8 (7, 10)
Ravlt III	11.94(2.12)	34	12 (10, 14)	11.09 (2.30)	149	11 (10, 13)	8.96 (2.67)	28	9 (7.25, 11)
Ravlt IV	12.56 (2.02)	34	13 (11, 14)	11.85 (2.12)	149	12 (11, 14)	10.18 (2.76)	28	10.5 (9, 12)
Ravlt V	13.29 (1.78)	34	14 (12.75, 15)	12.34 (2.07)	149	13 (11, 14)	10.61 (2.53)	28	11 (9, 12)
Ravlt Rec	6.41 (1.67)	34	7 (5, 7)	6.03 (1.85)	149	6 (5, 7)	4.43 (1.64)	28	5 (3, 5.75)
Ravlt VI	11.97 (2.71)	33	12 (11, 14)	10.86 (2.68)	149	11 (9, 13)	8.54 (3.02)	28	9 (7, 10.75)
Ravlt Delayed Recall	11.85 (2.54)	34	13 (10, 14)	10.46 (2.75)	149	11 (9, 13)	7.68 (2.64)	28	7.5 (6, 10)
Ravlt Word Recognition List A	13.26 (2.19)	34	14 (12, 15)	12.98 (2.20)	148	14 (12, 15)	10.64 (2.57)	28	10 (9, 13)
Ravlt Word Recognition List B	7.06 (2.44)	34	7 (5, 8.25)	6.71 (2.83)	148	6 (5, 9)	4 (2.93)	28	4 (2, 5.75)
RAVLT Word recognition Errors	2.61 (1.97)	28	2 (1, 3.75)	3.95 (2.97)	134	4 (2, 5)	2.71 (2.85)	28	2 (1, 4)
Ravlt (Total I-V)	55.06 (8.58)	34	57.5 (48.5, 62)	51.04 (8.56)	149	51 (45, 58)	43.78 (10.48)	28	43 (38.5, 49.75)
Hayling Errors A	3.65 (7.10)	34	3 (0, 3)	3.60 (4.87)	154	3 (0, 6)	4.39 (5.69)	28	1.5 (0, 6)
Hayling Errors B	2.15 (4.47)	34	1 (0, 2.25)	4.84 (6.91)	153	2 (1, 4)	3.64 (5.55)	28	2 (1, 3)
Hayling Time A	16.34 (8.34)	34	12.94 (11.09, 19.47)	22.44 (16.82)	152	17.33 (13.46, 22.93)	27.24 (17.78)	28	22.22 (15.42, 32.56)
Story Immediate	10.91 (3.81)	34	10.75 (8.12, 13.5)	8.91 (3.29)	152	8.75 (6.77, 1.5)	6.95 (3.09)	22	6.75 (4.75, 8.75)
Story Delayed	10.04 (3.26)	34	10.5 (7.75, 12.5)	7.78 (3.20)	152	7.5 (5.62, 10)	6.14 (3.09)	22	6 (3.75, 7.62)
Verbal Fluency Total	40.53 (9.63)	34	42 (33.25, 48.25)	37.95 (12.01)	150	38 (28.75, 45)	28.09 (8.32)	23	26 (23, 35)
Nart-Fsiq Difference	-0.23 (11.14)	34	0 (-7.0, 7.25)	0.039 (12.11)	152	0.5 (-6.75, 9)	5.87 (8.40)	24	4.5 (-0.5, 11.75)
Digits Forwards	8.23 (2.26)	34	8 (6, 10)	8.78 (5.89)	157	8 (7, 10)	7.44 (2.13)	27	7 (6, 9)
Digits Backwards	7.79 (2.31)	34	7 (6, 9.25)	7.18 (2.30)	157	7 (6, 8)	5.74 (2.36)	27	5 (4, 8)
RBMT Standardised	22..62 (1.39)	34	22 (21.75, 24)	21.49 (2.39)	152	22 (20, 24)	19.54 (4.02)	22	20.5 (17, 23.25)
RBMT Screening Score	10.97 (1.14)	34	11 (10, 12)	10.34 (1.46)	152	10 (9.25, 12)	9.14 (2.51)	22	9.5 (7, 11.25)

Variables	CONTROLS			HIGH RISK			PATIENTS		
	Mean (sd)	N	Median (25^{th}, 75th P)	Mean (sd)	N	Median (25th, 75th P	Mean (sd)	N	Median(25th P, 75th P)
Total	5.79 (10.03)	34	3 (0.75, 5.25)	8.46 (10.31)	153	4 (1, 14)	8.04 (8.97)	28	4.5 (1, 15)
Scolp	-1.35 (3.59)	31	-2 (-4, 1)	-1.46 (2.96)	146	-2 (-3, 0.25)	0.58 (3.21)	26	1 (-2, 3.25)
Rey trial v-trial i	6 (1.87)	34	6 (4, 7)	6.01 (2.28)	149	6 (5, 7.5)	4.89 (2.35)	28	5 (3, 6.75)
Rey trial I- list B	0.88 (1.77)	34	0 (0, 2)	0.31 (2.28)	149	1 (-1, 2)	1.28 (2.12)	28	1 (0, 2)
Rey trial v-trial vi	1.30 (1.42)	33	1 (0.5, 2)	1.48 (1.90)	149	1 (0, 3)	2.07 (1.80)	28	3 (1, 3)
Rey trial vi- trial I	4.67 (2.52)	33	5 (3, 6.5)	4.52 (2.75)	149	5 (3, 7)	2.82 (2.71)	28	(1, 4.75)
Stroop condition 3-condition 1	11.07 (4.96)	32	10.6 (8.4, 13.57)	13.54 (5.37)	146	12.65 (9.7, 16.37)	15.57 (4.51)	24	15.5 (12.55, 18.42)
WMS-R VR 1 – WMS-R VR 2	2.72 (2.65)	32	2 (1, 4)	2.64 (3.69)	144	2 (1, 4)	4.18 (4.22)	28	3.5 (0.25, 7)
RAVLT VI	150.39 (57.14)	33	144 (121, 196)	125.06(55.28)	149	121 (81, 169)	81.67 (49.26)	28	81 (49, 115.75)
Hayling Time A	0.98 (0.15)	34	0.94 (0.88, 1.09)	1.06 (0.17)	152	1.05 (0.95, 1.14)	1.14 (0.16)	28	1.13 (1.01, 1.25)
Hayling Time B	1.20 (0.21)	32	1.24 (1.0, 1.32)	1.24 (0.19)	151	1.25 (1.10, 1.40)	1.31 (0.14)	28	1.33 (1.19, 1.40)
Hayling B-A	2.40 (1.68)	31	2.9 (1.28, 3.38)	2.76 (1.18)	125	2.88 (2.20, 3.64)	2.89 (1.0)	24	3.24 (2.28, 3.53)
WMS-R Vis Rep 1	2059398.4 (556314.84)	32	208516 (1679616, 2560000)	1650547.7 (629418.33)	144	1679616 (1185921, 2085136)	1429473 (631107.05)	28	1336336 (1082912.3, 1874161)
WMS-R Vis Rep 2	1720693.6 (693399.93)	32	1676916 (1264957, 2313441)	1324953.4 (664660.60)	144	1336336 (810000, 1874161)	969213.68 (660686.95)	28	923521 (531441, 1500625)
RAVLT word recognition errors	150 (0.61)	28	1.41 (1, 1.93)	1.83 (0.78)	138	2 (1.41, 2.24)	1.36 (0.95)	28	1.41 (1, 2)

Appendix 2, Matrix 4.1. Correlation matrix of neuropsychological test results for the control group

	FSIQ	VF 'F'	VF 'A'	VF 'S'	ANIMALS	STROOP3	SPOTWRS	SPEEDCS	SCOLP	TOKENT	VR1	VR2	RAVLTI	RAVLTII
FSIQ	1													
VF 'F'	0.353*	1												
VF 'A'	0.383*	0.455**	1											
VF 'S'	0.454**	0.474**	0.531**	1										
ANIMALS	0.544**	0.279	0.456**	0.324	1									
STROOP3	-0.382	-0.313	-0.370*	-0.386	-0.249	1								
SPOTWRS	0.621**	0.231	0.124	0.329	0.137	-0.191	1							
SPEEDCS	0.378*	0.428*	0.336	0.279	0.275	-0.517**	0.184	1						
SCOLP	0.052	-0.237	-0.221	-0.040	-0.168	0.342	0.472**	-0.780**	1					
TOKENT	0.167	0.416*	0.315	0.357*	0.194	-0.253	0.059	0.444*	-0.375*	1				
VR1	0.389*	0.318	0.121	0.191	0.463**	-0.153	0.385*	-0.018	0.262	-0.047	1			
VR2	0.479**	0.258	0.196	0.287	0.251	-0.055	0.528**	-0.156	0.481**	-0.031		1		
RAVLTI	0.310	0.171	0.290	0.271	0.304	-0.456**	0.177	0.588**	-0.414*	0.210	-0.071	-0.098	1	
RAVLTII	0.497**	0.307	0.337	0.262	0.419*	-0.140*	0.308	0.507**	-0.266	0.307	0.072	0.041	0.598**	1
RAVLTIII	0.554**	0.159	0.261	0.231	0.458**	-0.324	0.190	0.446*	-0.277	0.319	0.116	-0.004	0.657**	0.806**
RAVLTIV	0.476**	0.056	0.210	0.265	0.371*	-0.408*	0.396*	0.457**	-0.158	0.135	0.180	0.201	0.610**	0.692**
RAVLTV	0.165	-0.046	0.094	0.108	0.449*	-0.308	0.030	0.134	-0.045	-0.189	0.166	0.066	0.482*	0.469*
RAVLTREC	0.317	0.203	0.035	0.101	0.049	-0.116	0.228	0.365*	-0.184	0.164	0.093	-0.051	0.525**	0.344*
RAVLTVI	0.390*	-0.218	-0.004	0.040	0.417*	-0.249	0.243	0.249	-0.072	0.034	0.137	0.080	0.491**	0.552**
RAVLDELR	0.262	-0.005	0.062	0.039	0.310	-0.299	0.038	0.223	-0.142	-0.162	-0.076	-0.144	0.563*	0.572*
REY	0.505**	0.158	0.279	0.277	0.471**	-0.428*	0.282	0.517**	-0.283	0.207	0.111	0.048	0.793**	0.866**
ERRSAC	0.164	-0.035	0.103	-0.183	0.109	0.005	-0.164	0.002	-0.123	-0.208	-0.050	0.017	0.074	-0.049
ERRSAB	-0.176	0.009	-0.042	0.025	-0.390*	0.205	0.043	-0.226	0.236	-0.174	-0.069	-0.036	-0.127	-0.198
TOTAL	0.105	0.081	0.159	-0.033	-0.052	0.067	-0.058	-0.004	-0.044	-0.166	-0.045	-0.026	0.058	-0.122
HTIMEA	0.076	-0.190	-0.384	-0.324	-0.174	0.074	-0.093	-0.309	0.218	-0.303	-0.145	0.023	-0.055	-0.046
RBMTSTAN	0.116	0.071	0.289	0.087	0.140	-0.070	-0.077	0.190	-0.204	0.182	0.035	-0.132	0.357*	-0.046
RBMTSCRE	0.141	0.072	0.302	0.049	0.155	-0.093	-0.074	0.170	-0.188	0.094	0.054	-0.080	0.369*	-0.024
STORYIM	0.603**	0.313	0.453**	0.432*	0.358*	-0.306	0.501**	0.613**	-0.229	0.385*	0.062	0.149	0.527**	0.599**
STORYDEL	0.578**	0.315	0.423*	0.403*	0.291	-0.345*	0.461**	0.621**	-0.260	0.389*	0.045	0.061	0.410*	0.518**

Appendix 2, Matrix 4.1. Correlation matrix of neuropsychological test results for the control group

	FSIQ	VF 'F'	VF 'A'	VF 'S'	ANIMALS	STROOP3	SPOTWRS	SPEEDCS	SCOLP	TOKENT	VR1	VR2	RAVLTI	RAVLTII
FAS	0.491**	0.795**	0.795**	0.841**	0.429*	-0.438*	0.288	0.425*	-0.198	0.456**	0.262	0.307	0.299	0.369*
DIGITF	0.474**	0.259	0.187	0.498**	0.168	-0.181	0.130	0.521**	-0.389*	0.388*	-0.028	-0.036	0.262	0.283
DIGITB	0.330	-0.009	0.070	0.293	-0.057	-0.275	0.217	0.226	-0.065	-0.108	0.170	0.046	0.155	0.062
RAVLWRA	-0.370*	-0.146	-0.082	0.355*	-0.161	-0.037	0.209	-0.177	-0.228	0.471*	0.111	0.040	0.471*	0.275
RAVLWRB	0.128	0.061	0.084	0.047	0.270	-0.337	0.006	0.307	-0.283	0.066	-0.067	-0.340	0.621**	0.527**
RAVLWRE	-0.333	-0.164	-0.021	-0.033	0.025	0.357	-0.435*	-0.059	-0.270	0.034	-0.261	-0.160	-0.189	-0.173

Appendix 2, Matrix 4.1. Correlation matrix of neuropsychological test results for the control group

	NART	INFOR	DSPAN	VOCAB	ARITH	COMPRE	SIMILAR	PIC COMP	PICARR	BLOCKS	OA	DSYMBOL	VIQ	PIQ
NART	1													
INFOR	0.694**	1												
DSPAN	0.479**	0.338	1											
VOCAB	0.727**	0.683**	0.385*	1										
ARITH	0.497**	0.712**	0.569**	0.576**	1									
COMPRE	0.530**	0.437**	0.396**	0.687**	0.510**	1								
SIMILAR	0.658**	0.613**	0.341*	0.717**	0.603**	0.636**	1							
PIC COMP	0.290	0.149	0.131	0.205	0.282	0.282	0.465**	1						
PIC ARR	0.395*	0.444**	0.364*	0.399*	0.639**	0.040*	0.506**	0.348*	1					
BLOCKS	0.138	0.427*	0.011	0.325	0.453**	0.266	0.402*	0.343*	0.351*	1				
OA	0.478**	0.601**	0.128	0.468**	0.577**	0.346*	0.475**	0.437**	0.514**	0.588**	1			
DSYMBOL	0.210	0.135	0.444**	0.236	0.334	0.288	0.187	0.174	0.498**	0.152	0.288	1		
VIQ	0.688**	0.806**	0.577**	0.788*	0.860**	0.674**	0.782**	0.235	0.582**	0.483**	0.608**	0.325	1	
PIQ	0.391*	0.487**	0.258	0.422*	0.620**	0.375*	0.544**	0.572**	0.749**	0.726**	0.819**	0.583**	0.640**	1
FSIQ	0.616*	0.745**	0.462**	0.687**	0.840**	0.580**	0.743**	0.426*	0.713**	0.660**	0.783**	0.472**	0.923**	0.881**
VF 'F'	0.451*	0.299	0.156	0.431*	0.259	0.231	0.300	0.001	0.392*	0.067	0.220	0.289	0.352*	0.268
VF 'A'	0.179	0.264	0.094	0.315	0.286	0.199	0.220	-0.060	0.317	0.287	0.296	0.494**	0.313	0.407*
VF 'S'	0.405*	0.335	0.460**	0.398*	0.392*	0.406*	0.249	0.106	0.384*	0.174	0.266	0.564**	0.443**	0.404*
ANIMALS	0.112	0.094	0.063	0.300	0.447**	0.273	0.391*	0.329	0.435*	0.498**	0.446**	0.559**	0.371*	0.643**
STROOP3	-0.456**	-0.193	-0.306	-0.340	-0.212	-0.290	-0.288	-0.121	-0.273	-0.184	-0.408*	-0.402*	-0.317	-0.396*
SPOTWRS	0.604**	0.777**	0.218	0.648**	0.539**	0.518**	0.631**	0.383*	0.408*	0.379*	0.575**	0.040	0.653**	0.449**
SPEEDCS	0.489**	0.175	0.449**	0.385	0.310	0.257	0.406*	0.249	0.461**	-0.196	0.269	0.567	0.370*	0.349
SCOLP	-0.072	0.340	-0.271	0.068	0.065	0.102	0.024	0.021	-0.152	0.418*	0.128	-0.483**	0.079	-0.026
TOKENT	0.242	0.071	0.154	0.260	0.127	0.253	0.242	0.201	0.249	-0.154	0.046	0.227	0.147	0.134
VR1	0.228	0.154	0.125	0.331	0.159	0.289	0.413*	0.379*	0.236	0.562**	0.403*	0.196	0.247	0.460**
VR2	0.313	0.386*	0.077	0.613**	0.265	0.521**	0.534**	0.152	0.321	0.538**	0.361*	-0.033	0.504**	0.366**
RAVLTI	0.506**	0.270	0.259	0.353*	0.286	0.194	0.209	0.053	0.308	0.019	0.202	0.425*	0.289	0.283
RAVLTII	0.422**	0.348**	0.227	0.356*	0.554**	0.329	0.317	0.291	0.407*	0.147	0.402*	0.416*	0.435*	0.451**
RAVLTIII	0.333	0.342*	0.264	0.319	0.525**	0.275	0.272	0.270	0.411*	0.382*	0.437**	0.478**	0.441**	0.575**
RAVLTIV	0.403*	0.315	0.412*	0.470**	0.499**	0.515**	0.422*	0.221	0.258	0.246	0.302	0.393*	0.512**	0.366*

Appendix 2, Matrix 4.1. Correlation matrix of neuropsychological test results for the control group

	NART	INFOR	DSPAN	VOCAB	ARITH	COMPRE	SIMILAR	PIC COMP	PICARR	BLOCKS	OA	DSYMBOL	VIQ	PIQ
RAVLTV	0.102	-0.082	0.069	0.132	0.130	0.184	0.092	0.186	0.010	0.236	0.099	0.396*	0.072	0.249
RAVLTREC	0.242	0.372*	0.253	0.084	0.302	-0.059	0.112	0.039	0.458**	0.105	0.231	0.343**	0.237	0.344*
RAVLTVI	0.209	0.100	0.228	0.236	0.386*	0.260	0.302	0.372*	0.172	0.371*	0.280	0.323	0.341	0.408*
RAVLDELR	0.194	0.115	0.030	0.019	0.215	-0.080	0.130	0.112	0.094	0.211	0.168	0.320	0.156	0.290
REY	0.417*	0.307	0.309	0.396*	0.506**	0.361*	0.326	0.251	0.361*	0.252	0.369*	0.502**	0.448**	0.479**
ERRSAC	-0.177	0.013	-0.124	0.093	0.111	-0.111	0.068	-0.191	0.095	0.159	0.007	-0.133	0.168	0.064
ERRSAB	0.176	0.185	0.088	0.198	-0.009	0.045	-0.119	-0.139	-0.124	-0.119	-0.153	-0.217	-0.065	-0.302
TOTAL	-0.003	0.153	0.015	0.231	0.126	-0.017	0.039	-0.217	0.100	0.077	0.001	-0.121	0.162	-0.023
HTIMEA	0.034	0.135	-0.222	0.073	0.049	-0.041	-0.075	-0.022	-0.046	0.224	0.060	-0.238	0.055	0.036
RBMTSTAN	-0.059	0.048	0.031	-0.007	0.024	-0.081	-0.035	-0.055	0.111	0.133	0.154	0.267	0.062	0.229
RBMTSCRE	-0.033	0.071	-0.015	-0.020	-0.015	-0.089	0.022	-0.053	0.091	0.186	0.195	0.243	0.070	0.267
STORYIM	0.511**	0.580**	0.552**	0.497**	0.667**	0.396*	0.484**	0.107	0.599**	0.129	0.395*	0.441**	0.657**	0.455**
STORYDEL	0.474**	0.569**	0.473**	0.416	0.609**	0.295	0.454**	0.069	0.583**	0.072	0.440**	0.451**	0.599**	0.456**
FAS	0.435*	0.371*	0.306	0.473**	0.389*	0.351*	0.317	0.026	0.451**	0.212	0.320	0.555**	0.460**	0.443
DIGITF	0.376*	0.297	0.839**	0.372*	0.567**	0.373*	0.408*	0.162	0.468**	-0.042	0.017	0.519**	0.579**	0.288
DIGITB	0.408*	0.263	0.873**	0.243	0.421*	0.265	0.165	0.089	0.229	0.062	0.171	0.242	0.414*	0.183
RAVLWRA	0.140	-0.010	-0.027	0.138	0.108	-0.051	0.173	0.201	0.179	0.308	0.342*	0.279	0.202	0.450*
RAVLWRB	-0.340	0.018	-0.049	-0.085	0.168	-0.239	-0.050	0.140	0.146	0.145	0.180	0.259	-0.019	0.273
RAVLWRE	-0.473*	-0.370	0.062	-0.335	-0.176	-0.272	-0.461*	-0.086	-0.123	-0.289	-0.356	0.145	-0.318	-0.232

Appendix 2, Matrix 4.1. Correlation matrix of neuropsychological test results for the control group

	RAVLTIII	RAVLTIV	RAVLTV	RAVLTREC	RAVLTVI	RAVLDEL	REY	ERRSAC	ERRSAB	TOTAL	HTIMEA	RBMTSTAN	RBMTSCRE	STORYIM
RAVLTIII	1													
RAVLTIV	0.703**	1												
RAVLTV	0.494*	0.727*	1											
RAVLTREC	0.461**	0.271	0.125	1										
RAVLTVI	0.570**	0.773**	0.810*	0.140	1									
RAVLDELR	0.617*	0.593*	0.705*	0.342*	0.814**	1								
REY	0.891**	0.893**	0.710	0.417*	0.756**	0.747*	1							
ERRSAC	-0.049	-0.078	-0.105	0.014	-0.077	0.018	-0.004	1						
ERRSAB	-0.298	-0.264	-0.367*	-0.129	-0.361*	-0.344*	-0.312	0.370*	1					
TOTAL	-0.130	-0.176	-0.276	0.019	-0.240	-0.140	-0.123	0.902**	0.683**	1				
HTIMEA	0.054	-0.069	-0.009	0.110	0.016	0.050	-0.029	0.306	0.306	0.254	1			
RBMTSTAN	0.208	0.036	0.144	0.412*	0.059	0.229	0.134	0.088	-0.276	0.081	-0.230	1		
RBMTSCRE	0.202	0.066	0.189	0.428*	0.120	0.320	0.164	0.099	-0.319	0.058	-0.286	0.969**	1	
STORYIM	0.561**	0.574**	0.111	0.491**	0.300	0.312	0.588**	0.047	-0.160	0.060	-0.302	0.277	0.257	1
STORYDEL	0.442**	0.409*	-0.079	0.503**	0.137	0.188	0.440**	0.072	-0.072	0.107	-0.166	0.194	0.190	0.911**
FAS	0.266	0.220	0.095	0.142	-0.075	0.052		-0.069	-0.012	0.058	-0.365*	0.172	0.161	0.490**
DIGITF	0.326	0.409*	0.140	0.375*	0.184	0.090	0.348	-0.212	-0.046	-0.028	-0.179	0.082	0.026	0.568**
DIGITB	0.115	0.227	0.052	0.070	0.209	-0.026	0.134	-0.190	0.205	-0.032	-0.190	-0.038	-0.062	0.372*
RAVLWRA	0.522*	0.327	0.509*	0.214	0.588**	0.551*	0.474*	0.167	-0.333	0.013	0.008	0.420	0.420	0.150
RAVLWRB	0.635**	0.449**	0.427*	0.507**	0.521**	0.659**	0.661**	0.115	-0.195	0.007	0.098	0.226	0.242	0.276
RAVLWRE	-0.096	-0.101	0.077	-0.162	-0.088	-0.128	-0.124	-0.185	-0.238	-0.249	-0.105	0.032	-0.050	-0.099

	STORYDEL	FAS	DIGITF	DIGITB	RAVLWRA	RAVLWRB	RAVLWRE
STORYDEL	1						
FAS	0.467**	1					
DIGITF	0.475**	0.400*	1				
DIGITB	0.320	0.102	0.493**	1			
RAVLWRA	0.019	-0.132	-0.095	0.014	1		
RAVLWRB	0.269	0.077	0.036	-0.138	0.364*	1	
RAVLWRE	-0.170	-0.095	0.112	0.037	-0.073	-0.055	1

Appendix 2, Matrix 4.2. Correlation matrix of neuropsychological test results for the high risk group

	FSIQ	VF 'F'	VF 'A'	VF 'S'	ANIMALS	STROOP3	SPOTWRS	SPEEDCS	SCOLP	TOKENT	VR1	VR2	RAVLTI	RAVLTII
FSIQ	1													
VF 'F'	0.464**	1												
VF 'A'	0.516**	0.677**	1											
VF 'S'	0.355**	0.665**	0.688**	1										
ANIMALS	0.533**	0.434**	0.417**	0.336**	1									
STROOP3	-0.483**	-0.344**	-0.433**	-0.342**	-0.259**	1								
SPOTWRS	0.578**	0.411**	0.416**	0.269**	0.333**	-0.254**	1							
SPEEDCS	0.523**	0.358**	0.399**	0.294**	0.377**	-0.495**	0.486**	1						
SCOLP	-0.094	-0.055	-0.096	-0.099	-0.149	0.327**	0.286**	-0.695**	1					
TOKENT	0.244**	0.052	0.106	0.056	0.022	-0.188*	0.205*	0.221**	-0.089	1				
VR1	0.477**	0.289**	0.231**	0.186	0.235**	-0.426**	0.373**	0.250**	0.044	0.236**	1			
VR2	0.490**	0.405**	0.354**	0.245**	0.366**	-0.361**	0.384**	0.239**	0.057	0.220**		1		
RAVLTI	0.214**	0.179*	0.225**	0.293**	0.157	-0.267**	0.202*	0.185*	-0.020	0.055	0.193*	0.091	1	
RAVLTII	0.453**	0.206*	0.277**	0.231**	0.258**	-0.343**	0.288**	0.319**	-0.095	0.124	0.409**	0.368**	0.552**	1
RAVLTIII	0.412**	0.199*	0.292**	0.243**	0.251**	-0.293**	0.329**	0.408**	-0.168*	0.112	0.288**	0.282**	0.453**	0.719**
RAVLTIV	0.374**	0.179*	0.283**	0.217**	0.197*	-0.239**	0.270**	0.285**	-0.086	0.095	0.241**	0.262**	0.303**	0.594**
RAVLTV	0.389*	0.117	0.214*	0.230*	0.104	-0.266*	0.262*	0.277*	-0.127	0.162*	0.289**	0.329**	0.337**	0.558**
RAVLTREC	0.364**	0.176*	0.230**	0.219**	0.211*	-0.224**	0.292**	0.231**	0.000	0.189*	0.235**	0.253**	0.256**	0.360**
RAVLTVI	0.380**	0.106	0.219**	0.242**	0.214**	-0.261**	0.279**	0.280**	-0.068	0.064	0.179*	0.276**	0.324**	0.553**
RAVLDELR	0.379**	0.139	0.201**	0.171*	0.185*	-0.223**	0.305**	0.239*	-0.053	0.056	0.249**	0.321**	0.258**	0.541**
REY	0.459**	0.218**	0.330**	0.299**	0.242**	-0.353**	0.332**	0.372**	-0.123	0.136	0.352**	0.341**	0.639**	0.858**
ERRSAC	-0.226**	-0.178*	-0.096	-0.027	-0.118	0.087	-0.193*	-0.021	-0.146	-0.088	-0.097	-0.133	-0.076	-0.096
ERRSAB	-0.252**	-0.129	-0.122	-0.024	-0.131	0.093	-0.122	-0.095	0.010	-0.085	-0.108	-0.192*	-0.033	-0.137
TOTAL	-0.282**	-0.167*	-0.138	-0.034	-0.137	0.117	-0.189*	-0.081	-0.068	-0.102	-0.109	-0.176*	-0.061	-0.148
HTIMEA	-0.308**	-0.08	-0.223**	-0.079	-0.212**	0.039	-0.218**	-0.296**	0.141	-0.025	0.031	-0.023	-0.196*	-0.250**
RBMTSTAN	0.449**	0.233**	0.224**	0.088	0.236**	-0.266**	0.319**	0.334**	-0.127	0.185*	0.288**	0.292**	0.287**	0.464**
RBMTSCRE	0.416**	0.223**	0.194*	0.063	0.228**	-0.269**	0.293**	0.304**	-0.115	0.197*	0.285**	0.315**	0.262**	0.451**
STORYIM	0.500**	0.203*	0.212**	0.151	0.266**	-0.222**	0.408**	0.434**	-0.131	0.104	0.356**	0.362**	0.239**	0.415**
STORYDEL	0.521**	0.241**	0.238**	0.163*	0.329**	-0.292**	0.411**	0.459**	-0.155	0.090**	0.322**	0.298**	0.219**	0.432**

Appendix 2, Matrix 4.2. Correlation matrix of neuropsychological test results for the high risk group

	FSIQ	VF 'F'	VF 'A'	VF 'S'	ANIMALS	STROOP3	SPOTWRS	SPEEDCS	SCOLP	TOKENT	VR1	VR2	RAVLTI	RAVLTII
FAS	0.499**	0.889**	0.879**	0.890**	0.447**	-0.419**	0.409**	0.394**	-0.091	0.065	0.253**	0.376**	0.264**	0.265**
DIGITF	0.573**	0.309**	0.443**	0.281**	0.263**	-0.284**	0.453**	0.321**	0.020	0.244**	0.314**	0.296**	0.279**	0.306**
DIGITB	0.474**	0.342**	0.403**	0.275**	0.164*	-0.286**	0.326**	0.165*	0.092	0.209*	0.257**	0.207*	0.115	0.182*
RAVLWRA	0.280**	0.138	0.244**	0.120	0.104	-0.186*	0.178*	0.230**	-0.112	0.079	0.105	0.186*	0.273**	0.530**
RAVLWRB	0.131	0.181*	0.202*	0.186*	0.028	-0.195*	0.197*	0.174	-0.019	-0.140	0.227**	0.209*	0.269**	0.326**
RAVLWRE	-0.176*	-0.035	-0.085	0.117	-0.099	0.163	-0.098	-0.222*	0.175*	-0.086	-0.034	0.007	-0.065	-0.163

Appendix 2, Matrix 4.2. Correlation matrix of neuropsychological test results for the high risk group

	NART	INFOR	DSPAN	VOCAB	ARITH	COMPRE	SIMILAR	PIC COMP	PICARR	BLOCKS	OA	DSYMBOL	VIQ	PIQ
NART	1													
INFOR	0.575**	1												
DSPAN	0.524**	0.346**	1											
VOCAB	0.657**	0.668**	0.404**	1										
ARITH	0.513**	0.401**	0.559**	0.464**	1									
COMPRE	0.369**	0.479**	0.258**	0.614**	0.404**	1								
SIMILAR	0.526**	0.486**	0.292**	0.591**	0.395**	0.527**	1							
PIC COMP	0.355**	0.375**	0.167*	0.340**	0.301**	0.255**	0.329**	1						
PIC ARR	0.343**	0.294**	0.149	0.302**	0.328**	0.291**	0.257**	0.516**	1					
BLOCKS	0.450**	0.418**	0.372**	0.445**	0.497**	0.358**	0.443**	0.461**	0.398**	1				
OA	0.281**	0.261**	0.204*	0.338**	0.336**	0.296**	0.325**	0.455**	0.408**	0.562**	1			
DSYMBOL	0.371**	0.320**	0.324**	0.379**	0.461**	0.364**	0.275**	0.177*	0.238**	0.447**	0.284**	1		
VIQ	0.647**	0.713**	0.660**	0.718**	0.679**	0.659**	0.656**	0.341**	0.351**	0.509**	0.378**	0.446**	1	
PIQ	0.507**	0.466**	0.366**	0.477**	0.539**	0.412**	0.449**	0.688**	0.684**	0.780**	0.700**	0.596**	0.618**	1
FSIQ	0.643**	0.652**	0.580**	0.674**	0.675**	0.613**	0.613**	0.550**	0.577**	0.704**	0.602**	0.565**	0.911**	0.876**
VF 'F'	0.448**	0.394**	0.367**	0.430**	0.367**	0.269**	0.308**	0.167*	0.250**	0.357**	0.283**	0.302**	0.454**	0.362**
VF 'A'	0.524**	0.447**	0.472**	0.479**	0.376**	0.348**	0.359**	0.260**	0.296**	0.335**	0.256**	0.354**	0.506**	0.414**
VF 'S'	0.297**	0.219**	0.304**	0.290**	0.271**	0.270**	0.180*	0.151	0.223**	0.203*	0.193**	0.330**	0.319**	0.302**
ANIMALS	0.286**	0.478**	0.237**	0.433**	0.377**	0.418**	0.402**	0.370**	0.273**	0.405**	0.278**	0.232**	0.511**	0.455**
STROOP3	-0.368**	-0.152	-0.316**	-0.277**	-0.326**	-0.278**	-0.285**	-0.266**	-0.336**	-0.371**	-0.317**	-0.573**	-0.378**	-0.518**
SPOTWRS	0.676**	0.578**	0.429**	0.669**	0.474**	0.336**	0.478**	0.340**	0.304**	0.429**	0.286**	0.255**	0.601**	0.430**
SPEEDCS	0.596**	0.466**	-0.289**	0.353**	0.388**	0.357**	0.422**	0.416**	0.223**	0.306**	0.181*	0.475**	0.509**	0.458**
SCOLP	-0.101	-0.050	0.038	-0.044	-0.033	-0.123	-0.069	-0.167*	0.018	0.024	0.050	-0.313**	-0.067	-0.136
TOKENT	0.266**	0.103	0.263**	0.136	0.204*	0.106	0.255**	0.181*	0.132	0.149	0.153	0.152	0.240**	0.183*
VR1	0.385**	-0.192*	0.338**	0.354**	0.392**	0.390**	0.354**	0.250**	0.265**	0.589**	0.340**	0.325**	0.411**	0.454**
VR2	0.435**	0.303*	0.242**	0.366**	0.433**	0.426**	0.370**	0.367**	0.308**	0.578**	0.395**	0.317**	0.402**	0.503**
RAVLTI	0.143	0.113	0.222**	0.214**	0.100	0.147	0.099	0.001	0.140	0.131	0.015	0.322**	0.198*	0.208*
RAVLTII	0.334**	0.305**	0.267**	0.307**	0.305**	0.290**	0.259**	0.202*	0.255**	0.330**	0.208*	0.463**	0.404**	0.431**
RAVLTIII	0.343**	0.317**	0.217**	0.429**	0.219**	0.342**	0.272**	0.281**	0.112	0.280**	0.255**	0.422**	0.377**	0.363**
RAVLTIV	0.280**	0.301**	0.240**	0.349**	0.178*	0.252**	0.199*	0.213**	0.228**	0.242**	0.199*	0.396**	0.318**	0.331**

Appendix 2, Matrix 4.2. Correlation matrix of neuropsychological test results for the high risk group

	NART	INFOR	DSPAN	VOCAB	ARITH	COMPRE	SIMILAR	PIC COMP	PICARR	BLOCKS	OA	DSYMBOL	VIQ	PIQ
RAVLTV	0.304*	0.248*	0.298*	0.262*	0.264*	0.260**	0.214*	0.243**	0.198*	0.296*	0.263*	0.387**	0.326*	0.378*
RAVLTREC	0.263**	0.258**	0.295**	0.365**	0.218**	0.205*	0.086	0.279**	0.194*	0.234**	0.175*	0.212**	0.334**	0.293**
RAVLTVI	0.259**	0.252**	0.172*	0.241**	0.170*	0.204*	0.116	0.273**	0.273**	0.274**	0.277**	0.371**	0.271**	0.412**
RAVLDELR	0.273**	0.258**	0.183*	0.290**	0.204**	0.216**	0.153	0.235**	0.266**	0.352**	0.259**	0.347**	0.282**	0.414**
REY	0.354**	0.321**	0.307**	0.390**	0.266**	0.314**	0.260**	0.242**	0.223**	0.320**	0.240**	0.499**	0.402**	0.427**
ERRSAC	-0.018	-0.090	-0.157	-0.085	-0.174*	0.000	-0.174*	-0.203*	-0.200	-0.280**	-0.165*	-0.074	-0.132	-0.258**
ERRSAB	-0.092	-0.135	-0.153	-0.079	-0.165*	-0.086	-0.187*	-0.227**	-0.164*	-0.209**	-0.205*	-0.034	-0.214**	-0.238**
TOTAL	-0.080	-0.148	-0.182*	-0.122	-0.203*	-0.055	-0.204*	-0.246**	-0.205*	-0.285**	-0.208**	-0.076	-0.210**	-0.288**
HTIMEA	-0.247**	-0.256**	-0.199*	-0.292**	-0.203*	-0.287**	-0.169*	-0.109	-0.142	-0.064	-0.112	-0.184*	-0.329**	-0.233**
RBMTSTAN	0.297**	0.413**	0.230**	0.362**	0.301**	0.331**	0.377**	0.228**	0.226**	0.354**	0.261**	0.342**	0.426**	0.386**
RBMTSCRE	0.286**	0.396**	0.190**	0.350**	0.306**	0.327**	0.336**	0.205*	0.203*	0.332**	0.254**	0.329**	0.398**	0.350**
STORYIM	0.350**	-0.355**	0.204*	0.374**	0.353**	0.407**	0.294**	0.296**	0.374**	0.336**	0.305**	0.304**	0.446**	0.453**
STORYDEL	0.367**	0.332**	0.227**	0.369**	0.385**	0.378**	0.292**	0.269**	0.359**	0.320**	0.282**	0.343**	0.477**	0.464**
FAS	0.474**	0.394**	0.425**	0.446**	0.379**	0.330**	0.314**	0.212**	0.285**	0.334**	0.275**	0.370**	0.478**	0.402**
DIGITF	0.531**	0.365**	0.860**	0.465**	0.519**	0.323**	0.301**	0.212**	0.173*	0.346**	0.343**	0.306**	0.645**	0.389**
DIGITB	0.404**	0.261**	0.877**	0.273**	0.469**	0.133	0.199*	0.128	0.137	0.212**	0.174*	0.284**	0.518**	0.306**
RAVLWRA	0.205*	0.259**	0.096	0.252**	0.083	0.181*	0.156	0.095	0.078	0.210*	0.199*	0.297**	0.258**	0.250**
RAVLWRB	0.083	0.147	-0.031	0.261**	-0.002	0.130	0.185*	0.006	0.095	0.196*	0.125	0.153	0.084	0.149
RAVLWRE	-0.211*	-0.112	-0.092	-0.127	0.008	-0.044	-0.061	-0.104	-0.169	-0.065	-0.060	0.159	-0.135	-0.185*

Appendix 2, Matrix 4.2. Correlation matrix of neuropsychological test results for the high risk group

	RAVLTIII	RAVLTIV	RAVLTV	RAVLTREC	RAVLTVI	RAVLDEL	REY	ERRSAC	ERRSAB	TOTAL	HTIMEA	RBMTSTAN	RBMTSCRE	STORYIM
RAVLTIII	1													
RAVLTIV	0.706**	1												
RAVLTV	0.598**	0.668**	1											
RAVLTREC	0.387**	0.409**	0.399**	1										
RAVLTVI	0.672**	0.667**	0.709**	0.333**	1									
RAVLDELR	0.616**	0.681**	0.725**	0.349**	0.853**	1								
REY	0.880**	0.828**	0.792**	0.452**	0.734**	0.706**	1							
ERRSAC	-0.102	-0.075	-0.212**	-0.107	-0.129	-0.192*	-0.128	1						
ERRSAB	-0.100	-0.062	-0.199*	-0.137	-0.065	-0.121	-0.135	0.670**	1					
TOTAL	-0.136	-0.110	-0.243*	-0.158	-0.134	-0.204*	-0.167*	0.895**	0.906**	1				
HTIMEA	-0.167*	-0.107	-0.096	-0.085	-0.104	-0.085	-0.206*	0.072	0.093	0.098	1			
RBMTSTAN	0.430**	0.350**	0.299*	0.160	0.292**	0.326**	0.461**	-0.113	-0.039	-0.086	-0.234**	1		
RBMTSCRE	0.443**	0.361**	0.307**	0.140	0.295**	0.335**	0.459**	-0.082	-0.012	-0.054	-0.186*	0.959**	1	
STORYIM	0.302**	0.270**	0.253*	0.301**	0.269**	0.230**	0.372**	-0.029	-0.119	-0.097	-0.241**	0.356**	0.342**	1
STORYDEL	0.307**	0.267**	0.240*	0.297**	0.251**	0.252**	0.369**	-0.058	-0.086	-0.095	-0.298**	0.373**	0.348**	0.882**
FAS	0.272**	0.252**	0.200*	0.234**	0.210*	0.185*	0.315**	-0.113	-0.097	-0.123	-0.138	0.209*	0.188*	0.210*
DIGITF	0.253**	0.256**	0.301*	0.315**	0.182*	0.207*	0.347**	-0.111	-0.161*	-0.162*	-0.232**	0.233**	0.189*	0.218**
DIGITB	0.141	0.197*	0.254*	0.215**	0.156	0.151	0.221**	-0.199*	-0.149	-0.205*	-0.082	0.165*	0.130	0.126
RAVLWRA	0.605**	0.483**	0.505**	0.176*	0.601**	0.642**	0.603**	-0.108	-0.142	-0.169*	-0.098	0.360**	0.367**	0.214**
RAVLWRB	0.360**	0.334**	0.367**	0.378**	0.324**	0.331**	0.417**	-0.069	-0.118	-0.136	0.039	0.213**	0.211*	0.274**
RAVLWRE	-0.108	-0.279**	-0.070	-0.021	-0.241**	-0.168	-0.189*	0.071	-0.016	0.027	0.230**	0.105	-0.087	-0.041

	STORYDEL	FAS	DIGITF	DIGITB	RAVLWRA	RAVLWRB	RAVLWRE
STORYDEL	1						
FAS	0.238**	1					
DIGITF	0.211**	0.385**	1				
DIGITB	0.163*	0.380**	0.538**	1			
RAVLWRA	0.195*	0.185*	0.135	0.059	1		
RAVLWRB	0.202*	0.214**	-0.002	-0.012	0.428**	1	
RAVLWRE	-0.102	0.002	-0.079	-0.064	-0.046	0.228**	1

Appendix 4.3. Correlation matrix of neuropsychological test results for the first episode group

	FSIQ	VF 'F'	VF 'A'	VF 'S'	ANIMALS	STROOP3	SPOTWRS	SPEEDCS	SCOLP	TOKENT	VR1	VR2	RAVLTI	RAVLTII
FSIQ	1													
VF 'F'	0.591**	1												
VF 'A'	0.403	0.657**	1											
VF 'S'	0.631**	0.553**	0.526**	1										
ANIMALS	0.697**	0.416*	0.375	0.400	1									
STROOP3	-0.097	-0.267	-0.568*	-0.431	0.009	1								
SPOTWRS	0.783**	0.512*	0.343	0.613**	0.527*	-0.056	1							
SPEEDCS	0.496**	0.413	0.652**	0.592**	0.354	-0.662**	0.478*	1						
SCOLP	0.231	-0.063	-0.469*	-0.233	0.037	0.607**	0.410*	-0.605**	1					
TOKENT	0.353	0.188	0.043	0.146	0.059	-0.268	0.144	0.589**	-0.384	1				
VR1	0.670**	0.313	0.117	0.433*	0.686**	-0.009	0.491*	0.235	0.222	0.031	1			
VR2	0.632**	0.472*	0.292	0.385	0.539**	-0.134	0.319	0.368	-0.069	0.334	0.712**	1		
RAVLTI	0.618**	0.154	0.233	0.353	0.553**	-0.094	0.420*	0.412*	-0.032	0.226	0.466*	0.405*	1	
RAVLTII	0.432*	0.123	0.179	0.185	0.413	-0.036	0.308	0.385*	-0.121	0.185	0.191	0.272	0.744**	1
RAVLTIII	0.259	-0.071	-0.130	-0.166	0.247	0.006	0.039	0.272	-0.238	0.320	0.190	0.252	0.607**	0.670**
RAVLTIV	0.357	0.072	-0.028	0.085	0.168	-0.180	0.109	0.328	-0.243	0.474*	0.038	0.306	0.562**	0.710**
RAVLTV	0.375	0.257	0.169	0.233	0.202	-0.181	-0.162	0.270	-0.345	0.151	0.022	0.419*	0.339	0.508**
RAVLTREC	0.474*	0.021	0.219	0.409	0.234	-0.072	0.439*	0.204	0.170	-0.225	0.247	0.183	0.540*	0.447*
RAVLTVI	0.225	0.032	0.106	0.122	0.182	-0.387	-0.190	0.280	-0.465*	0.177	0.113	0.342	0.439*	0.548**
RAVLDELR	0.384*	0.134	0.130	0.142	0.300	-0.326	-0.084	0.452*	-0.515**	0.244	0.156	0.541**	0.398*	0.537**
REY	0.460*	0.116	0.096	0.136	0.355	-0.131	0.175	0.388*	-0.237	0.395	0.214	0.380*	0.802**	0.871**
ERRSAC	-0.025	-0.207	0.151	0.015	-0.193	-0.109	-0.022	-0.020	0.004	-0.344	0.001	-0.036	-0.039	-0.169
ERRSAB	0.041	-0.074	0.240	0.121	-0.001	0.053	0.087	-0.132	0.251	-0.410*	0.065	-0.203	0.126	0.087
TOTAL	0.031	-0.170	0.197	0.011	-0.127	-0.048	0.020	-0.083	0.137	-0.437*	-0.002	-0.119	0.007	-0.046
HTIMEA	-0.600**	-0.445*	-0.357	-0.245	-0.167	0.100	-0.324	-0.339	0.017	-0.333	-0.199	-0.357	-0.321	-0.124
RBMTSTAN	0.583**	0.314	0.381	0.210	0.308	-0.474*	0.471	0.479*	-0.205	0.237	0.333	0.706**	0.482*	0.307
RBMTSCRE	0.579**	0.240	0.340	0.152	0.344	-0.384	0.4558	0.462*	-0.193	0.184	0.370	0.720**	0.455*	0.367
STORYIM	0.696**	0.528*	0.179	0.183	0.324	-0.098	0.545*	0.036	0.456*	0.227	0.346	0.596**	0.373	0.272
STORYDEL	0.638**	0.475*	0.137	0.249	0.270	-0.039	0.405	-0.066	0.437	0.308	0.347	0.617**	0.375	0.247

Appendix 4.3. Correlation matrix of neuropsychological test results for the first episode group

	FSIQ	VF 'F'	VF 'A'	VF 'S'	ANIMALS	STROOP3	SPOTWRS	SPEEDCS	SCOLP	TOKENT	VR1	VR2	RAVLTI	RAVLTII
FAS	0.636**	0.854**	0.848**	0.840**	0.469*	-0.505*	0.569**	0.643**	-0.299	0161	0.371	0.451*	0.300	0.194
DIGITF	0.560**	0.143	0.227	0.380	0.168	-0.164	0.437*	0.256	0.168	0.315	0.364	0.172	0.187	-0.149
DIGITB	0.626**	0.219	0.261	0.337	0.414	-0.159	0.332	0.242	0.085	0.250	0.708**	0.535**	0.543**	0.224
RAVLWRA	0.316	0.158	0.220	0.249	0.266	-0.143	0.085	0.407*	-0.314	0.099	0.105	0.187	0.400*	0.506**
RAVLWRB	0.289	0.064	0.124	0.358	0.422*	0.152	0.358	0.367	-0.027	0.034	0.247	0.133	0.583**	0.499**
RAVLWRE	-0.067	0.152	0.074	0.182	0.060	0.292	-0.027	-0.052	0.084	-0.238	-0.140	-0.262	0.088	-0.014

Appendix 4.3. Correlation matrix of neuropsychological test results for the first episode group

	NART	INFOR	DSPAN	VOCAB	ARITH	COMPRE	SIMILAR	PIC COMP	PICARR	BLOCKS	OA	DSYMBOL	VIQ	PIQ
NART	1													
INFOR	0.752**	1												
DSPAN	0.608**	0.413*	1											
VOCAB	0.866**	0.832**	0.635**	1										
ARITH	0.566**	0.532**	0.679**	0.675**	1									
COMPRE	0.644**	0.769**	0.342	0.699**	0.379	1								
SIMILAR	0.774**	0.821**	0.493**	0.907**	0.555**	0.737**	1							
PIC COMP	0.265	0.491**	0.425*	0.479*	0.305	0.404*	0.392*	1						
PIC ARR	0.449*	0.593**	0.640**	0.585**	0.535**	0.653**	0.547**	0.534**	1					
BLOCKS	0.680**	0.494**	0.602**	0.626**	0.640**	0.374	0.583**	0.481*	0.538**	1				
OA	0.435*	0.381*	0.550**	0.452*	0.393*	0.317	0.357	0.616**	0.515**	0.720**	1			
DSYMBOL	0.285	0.020	0.312	0.236	0.263	0.166	0.337	-0.238	0.063	0.309	-0.035	1		
VIQ	0.836**	0.886**	0.662**	0.928**	0.712**	0.757**	0.893**	0.504**	0.673**	0.654**	0.517**	0.165	1	
PIQ	0.641**	0.578**	0.688**	0.678**	0.571**	0.558**	0.655**	0.628**	0.739**	0.904**	0.813**	0.294	0.745**	1
FSIQ	0.811**	0.814**	0.712**	0.885**	0.685**	0.720**	0.856**	0.584**	0.745**	0.798**	0.680**	0.221	0.958**	0.901**
VF 'F'	0.424	0.537**	0.194	0.453*	0.105	0.440*	0.472*	0.529*	0.567	0.495*	0.346	-0.191	0.491*	0.567**
VF 'A'	0.369	0.369	0.244	0.321	0.005	0.362	0.488*	0.117	0.384	0.288	0.139	0.300	0.326	0.394
VF 'S'	0.687**	0.476*	0.401	0.540**	0.306	0.273	0.561**	0.450*	0.271	0.526*	0.281	0.195	0.577**	0.538**
ANIMALS	0.428	0.558**	0.369	0.599**	0.329	0.413	0.540**	0.728**	0.397	0.607**	0.466*	0.035	0.607**	0.658**
STROOP3	-0.340	-0.049	-0.176	-0.144	-0.273	0.068	-0.264	0.103	-0.030	-0.148	0.157	-0.498*	-0.097	-0.095
SPOTWRS	0.695**	0.821**	0.466*	-0.737**	0.494*	0.554**	0.716**	0.496*	0.580**	0.515**	0.546**	-0.138	0.800**	0.604**
SPEEDCS	0.516**	0.481*	0.272	0.477*	0.255	0.451*	0.653**	0.212	0.382	0.442*	0.093	0.508**	0.400*	0.491*
SCOLP	0.100	0.282	0.182	0.210	0.228	0.068	-0.010	0.282	0.170	0.035	0.439	-0.657**	0.310	0.070
TOKENT	0.387	0.385	0.308	0.483*	0.362	0.416*	0.512*	0.072	0.438*	0.309	-0.124	0.444*	0.364	0.270
VR1	0.586**	0.467*	0.671**	0.604**	0.479*	0.390*	0.443*	0.730**	0.443*	0.693**	0.725**	0.165	0.574**	0.721**
VR2	0.544**	0.502**	0.465**	0.609**	0.559**	0.512**	0.564**	0.421*	0.320	0.721**	0.462*	0.333	0.585**	0.626**
RAVLTI	0.387	0.524**	0.459*	0.562**	0.407*	0.367	0.430*	0.658**	0.439	0.508**	0.334	0.371	0.577**	0.572**
RAVLTII	0.154	0.485*	0.076	0.482*	0.300	0.315	0.615**	0.295	0.191	0.297	0.087	0.304	0.423*	0.341
RAVLTIII	-0.051	0.211	0.049	0.262	0.194	0.342	0.319	0.252	0.331	0.189	0.075	0.391*	0.192	0.314
RAVLTIV	0.249	0.447*	0.138	0.455*	0.410*	0.355	0.493**	0.046	0.278	0.249	-0.138	0.419*	0.402*	0.226

Appendix 4.3. Correlation matrix of neuropsychological test results for the first episode group

	NART	INFOR	DSPAN	VOCAB	ARITH	COMPRE	SIMILAR	PIC COMP	PICARR	BLOCKS	OA	DSYMBOL	VIQ	PIQ
RAVLTV	0.203	0.238	0.221	0.316	0.444*	0.290	0.375	0.076	0.279	0.370	0.014	0.369	0.333	0.324
RAVLTREC	0.299	0.443*	0.260	0.412*	0.434*	0.349	0.471*	0.189	0.170	0.253	0.262	0.085	0.513**	0.314
RAVLTVI	0.133	0.167	0.122	0.210	0.303	0.270	0.346	-0.022	0.101	0.190	-0.177	0.610**	0.236	0.166
RAVLDELR	0.251	0.288	0.177	0.341	0.433*	0.321	0.432*	0.057	0.225	0.408*	-0.064	0.678**	0.340	0.344
REY	0.216	0.447*	0.206	0.483*	0.409*	0.401*	0.565**	0.227	0.331	0.371	0.067	0.453*	0.440*	0.406*
ERRSAC	-0.224	-0.272	-0.034	-0.359	0.036	-0.114	-0.209	-0.128	-0.089	0.101	0.216	-0.063	-0.123	0.097
ERRSAB	-0.159	-0.039	0.146	-0.099	0.159	-0.150	-0.103	0.014	-0.067	-0.013	0.115	-0.413*	-0.008	0.014
TOTAL	-0.230	-0.163	0.036	-0.288	0.129	-0.118	-0.173	-0.096	-0.071	0.059	0.185	-0.238	-0.055	0.080
HTIMEA	-0.305	-0.394*	-0.469*	-0.429*	-0.449*	-0.442*	-0.490**	-0.346	-0.574**	-0.567**	-0.406*	-0.138	-0.536**	-0.647**
RBMTSTAN	0.448*	0.437*	0.331	0.447*	0.489*	0.510*	0.605**	0.192	0.332	0.387	0.176	0.511*	0.554**	0.376
RBMTSCRE	0.437	0.421	0.334	0.464*	0.506*	0.519*	0.598**	0.210	0.308	0.405	0.224	0.549*	0.550**	0.386
STORYIM	0.394	0.744**	0.526*	0.647**	0.709**	0.413	0.552**	0.362	0.512*	0.524*	0.338	-0.063	0.747**	0.464*
STORYDEL	0.436	0.695**	0.519*	0.660**	0.686**	0.431	0.520**	0.364	0.473*	0.439*	0.231	-0.097	0.735**	0.364
FAS	0.581**	0.538**	0.334	0.516*	0.170	0.413	0.595**	0.427*	0.466*	0.513*	0.297	0.129	0.547**	0.584**
DIGITF	0.532**	0.342	0.844**	0.490**	0.521**	0.322	0.360	0.285	0.602**	0.385*	0.304	0.107	0.599**	0.491**
DIGITB	0.471*	0.303	0.879**	0.570**	0.593**	0.209	0.458*	0.407*	0.487*	0.615**	0.595**	0.422*	0.537**	0.667**
RAVLWRA	0.156	0.340	0.069	0.294	0.148	0.349	0.450*	0.155	0.263	0.213	0.008	0.415*	0.320	0.324
RAVLWRB	0.093	0.184	0.098	0.207	0.106	0.118	0.398*	0.324	0.111	0.327	0.223	0.139	0.222	0.336
RAVLWRE	-0.306	-0.081	0.001	-0.188	-0.219	-0.140	-0.043	0.133	-0.094	-0.008	0.019	-0.240	-0.100	-0.010

Appendix 4.3. Correlation matrix of neuropsychological test results for the first episode group

	RAVLTIII	RAVLTIV	RAVLTV	RAVLTREC	RAVLTVI	RAVLDEL	REY	ERRSAC	ERRSAB	TOTAL	HTIMEA	RBMTSTAN	RBMTSCRE	STORYIM
RAVLTIII	1													
RAVLTIV	0.688**	1												
RAVLTV	0.377*	0.686**	1											
RAVLTREC	0.080	0.162	0.312	1										
RAVLTVI	0.529**	0.725**	0.740**	0.257	1									
RAVLDELR	0.537**	0.700**	0.821**	0.255	0.867**	1								
REY	0.829**	0.899**	0.709**	0.315	0.709**	-0.745**	1							
ERRSAC	-0.182	-0.341	-0.126	0.230	-0.151	-0.143	-0.243	1						
ERRSAB	-0.232	-0.111	0.054	0.566**	0.001	-0.127	-0.056	0.548**	1					
TOTAL	-0.179	-0.256	-0.024	0.470*	-0.054	-0.128	-0.142	0.883**	0.839**	1				
HTIMEA	-0.037	-0.061	-0.326	-0.110	0.028	-0.128	-0.182	-0.116	0.042	-0.110	1			
RBMTSTAN	0.386	0.288	0.326	0.131	0.490*	0.475*	0.388	0.200	-0.110	0.125	-0.109	1		
RBMTSCRE	0.428*	0.340	0.397	0.143	0.523*	0.533*	0.452*	0.192	-0.127	0.099	-0.096	0.969**	1	
STORYIM	0.059	0.415	0.276	0.222	0.295	0.223	0.357	-0.114	0.212	0.095	-0.388	0.413	0.363	1
STORYDEL	0.029	0.432*	0.444*	0.156	0.298	0.325	0.360	-0.240	-0.041	-0.152	-0.467*	0.429*	0.393	0.879**
FAS	-0.148	0.053	0.234	0.271	0.105	0.152	0.138	0.025	0.118	0.042	-0.404	0.368	0.303	0.344
DIGITF	-0.192	-0.024	0.039	0.201	-0.098	-0.086	-0.046	0.019	0.200	0.114	-0.522**	0.115	0.072	0.288
DIGITB	0.201	0.209	0.306	0.231	0.235	0.330	0.337	-0.107	0.050	-0.071	-0.313	0.420	0.439*	0.521*
RAVLWRA	0.462*	0.505**	0.487**	0.230	0.547**	0.577**	0.575**	-0.191	-0.175	-0.175	-0.029	0.306	0.327	0.051
RAVLWRB	0.312	0.082	0.024	0.246	0.044	0.098	0.352	0.158	0.091	0.188	-0.167	0.345	0.276	0.013
RAVLWRE	-0.270	-0.275	-0.136	0.107	-0.238	-0.189	-0.167	0.105	0.316	0.256	-0.172	-0.324	-0.392	0.118

	STORYDEL	FAS	DIGITF	DIGITB	RAVLWRA	RAVLWRB	RAVLWRE
STORYDEL	1						
FAS	0.338	1					
DIGITF	0.347	0.300	1				
DIGITB	0.442*	0.322	0.508**	1			
RAVLWRA	0.049	0.223	-0.148	0.242	1		
RAVLWRB	-0.116	0.228	-0.064	0.210	0.507**	1	
RAVLWRE	-0.067	0.163	0.075	0.005	0.120	0.508**	1

Appendix 2. Matrix 4.4 Evaluation of linear predictors

The evaluation of the linear predictors is presented here in Matrix 4.4. Data is presented for a sample of 14 subjects. Subjects 1-4 are controls, 5-12 are high-risk subjects, and 13-14 are first episode patients.They represent a random sample of subjects from each group who were deleted from the database in order to test the linear predictors. The linear predictors were calculated once data for the 14 subjects were removed. By removing a sample the linear predictors could be used to predict the values for these subjects where the true values were known, and the discrepancy between the actual and predicted values could be calculated in order to evaluate the models. The observed and predicted values and the discrepancies for the random sample are displayed. The predicted, observed, observed minus predicted (obs-pred), and observed minus mean (obs-mean) are displayed. The predicted values were calculated according to the linear predictors as outlined in Chapter four, Table 4.4, the observed value represents the subjects true score obtained on the test, the observed minus mean is the observed score minus the mean for that variable for each group (displayed at the end of the table). The observed minus predicted value is a residual score, the amount by which the predictor was inaccurate. Observed minus mean represents the degree of inaccuracy occurring if the mean was used instead of the predicted value. A comparison of the difference scores evaluates which method was most accurate. The one with the smallest deviation was deemed best.

The legend presented in the matrix can be defined;
VFF, VFA, and VFS= verbal fluency 'f', 'a', 's', respectively.
NART= National Adult Reading Test
Animals= Semantic category of verbal fluency, animals
FAS= Total 'f', 'a', 's', combined.
Stroop3= time taken to complete Stroop3
Spotws=Spot the word scaled score
Speedcs=Speed of comprehension scaled score
Scolp= Speed and capacity of language processing test
RAVLSIX= Recall of ravlt (transformed back to original scale)
VR1=Visual Reproductions 1 to power of 4 (transformed back to original scale)

VR2=Visual Reproductions 2 to power of 4 (transformed back to original scale)

In a qualitative evaluation of the linear predictors, counting how many times the observed- predicted was less than the observed mean, i.e. the accuracy of both the predicted score and the mean of the variable for each group in predicting the true score.

13 variables were examined in total;
For controls 77% of the time the linear predictor was better than the mean, the figures were 62%, and 82% for the high-risk group and the patient group respectively.

Although this does not give a measure of the magnitude of the deviations it suggests that the linear predictors are more accurate than simply substituting the mean. There are many methods for data imputation available in the statistical and mathematical literature, and this is rather a simplistic attempt to improve the accuracy of the estimations, but one better than simply using the mean.

Appendix 2, Matrix 4.4. Evaluation of the linear predictors

	1	predicted	observed	obs-pre	obs-mean	2 predicted	observed	obs-pre	obs-mean	3 predicted	observed	obs-pre	obs-mean	4 predicted	observed	obs-pre	obs-mean
	vff control	12,917	7	-5,917	-6,73	14,481	15	0,519	1,27	12,135	9	-3,135	-4,73	14,481	14	-0,481	0,27
	vfa control	10,384	6	-4,384	-5,44	8,149	14	5,851	2,56	11,129	10	-1,129	-1,44	10,384	14	3,616	2,56
	vfs control	13,098	8	-5,098	-7,35	14,934	14	-0,934	-1,35	14,07	9	-5,07	-6,35	15,798	16	0,202	0,65
	nart con	81,761	102	20,239	-3,23	107,735	107	-0,735	1,77	99,077	87	-12,077	-18,23	107,735	106	-1,735	0,77
	animals c	12,998	12	-0,998	-5,97	16,84	13	-3,84	-4,97	15,032	12	-3,032	-5,97	18,648	15	-3,648	-2,97
	fas control	34,687	21	-13,687	-19,53	39,26	43	3,74	2,47	37,108	28	-9,108	-12,53	41,412	44	2,588	3,47
	stroop3 c	22,054	23,5	1,446	2,19	22,804	27	4,196	5,69	23,554	27,2	3,646	5,89		21,4		0,09
	spotws c	10,141	7	-3,141	-4,03	11,569	12	0,431	0,97	9,427	9	-0,427	-2,03	11,569	11	-0,569	-0,03
	speedcs c	11,591	11	-0,591	-1,37	9,641	10	0,359	-2,37	12,241	9	-3,241	-3,37	11,591			
	scolp c	-0,421	-4	-3,579	-5,35	1,466	2	0,534	0,65	-1,05	0	1,05	-1,35	-0,421			
	ralvsix c	8,149539864	8	-0,14953986	-4,26336006	8,149539864	7	-1,14953986	-5,26336006	13,11887953	14	0,881120475	1,736639938	11,69935896	11	-0,69935896	-1,26336006
	vr1 c	34,56691542	33	-1,56691542	-4,88218945	37,91998206	37	-0,91998206	-0,88218945	38,33234439	39	0,667655612	1,117810551	38,7318124	38	-0,7318124	0,117810551
	vr2 c	31,83851586	25	-6,83851586	-11,2181206	36,22373807	37	0,776261933	0,781879353	36,73444106	36	-0,73444106	-0,21812065	37,22469056	39	1,775309444	2,781879353
		5				6				7				8			
		predicted	observed	obs-pre	obs-mean	predicted	observed	obs-pre	obs-mean	predicted	observed	obs-pre	obs-mean	predicted	observed	obs-pre	obs-mean
	vff hr	11,533	8	-3,533	-4,81	17,131	21	3,869	8,19	14,332	8	-6,332	-4,81	13,399	12	-1,399	-0,81
	vfa hr	11,287	6	-5,287	-4,71	12,778	23	10,222	12,29	11,287	7	-4,287	-3,71	9,796	5	-4,796	-5,71
	vfs hr	14,265	12	-2,265	-2,4	17,265	21	3,735	6,6	14,015	7	-7,015	-7,4	15,015	5	-10,015	-9,4
	nart hr	94,091	82	-12,091	-16,36	112,145	112	-0,145	13,64	103,118	97	-6,118	-1,36	100,109	102	1,891	3,64
	animals hr	15,296	16	0,704	0,43	20,024	16	-4,024	0,43	14,902	10	-4,902	-5,57	16,478	22	5,522	6,43
	fas hr	37,248	26	-11,248	-11,95	48,072	65	16,928	27,05	36,346	22	-14,346	-15,95	39,954	22	-17,954	-15,95
	stroop3 hr	24,536	23,8	-0,736	0,19	20,221	18,2	-2,021	-5,41	27,988	30	2,012	6,39	24,536	25,3	0,764	1,69
	spotws hr	8,456	6	-2,456	-3,46	13,052	13	-0,052	3,54	10,754	11	0,246	1,54	9,988	9	-0,988	-0,46
	speedcs hr	11,079	10	-1,079	-0,93	13,375	15	1,625	4,07	11,653	6	-5,653	-4,93	9,931	10	0,069	-0,93
	scolp hr	-1,917	-4	-2,083	-5,46	-2,958	-2	0,958	-3,46	-1,917	5	6,917	3,54	-0,876	-1	-0,124	-2,46
	ralvsix c	13,11887953	14	0,881120475	2,816977153	10,84550598	11	0,154494018	-0,18302285	12,33268016	12	-0,33268016	0,816977153	13,01268612	10	-3,01268612	-1,18302285
	vr1 c	36,11916365	37	0,880836349	1,156778202	40,70272329	39	-1,70272329	3,156778202	36,58049656	37	0,419503436	1,156778202	37,25758527	40	2,742414734	4,156778202
	vr2 c	33,92818046	37	3,07181954	3,072636005	39,91256491	32	-7,91256491	-1,92736399	34,98219166	33	-1,98219166	-0,92736399	35,81938268	38	2,180617316	4,072636005
		9				10				11				12			
		predicted	observed	obs-pre	obs-mean	predicted	observed	obs-pred	obs-mean	predicted	observed	obs-pre	obs-mean	predicted	observed	obs-pre	obs-mean
	vff hr	14,332	15	0,668	2,19	12,466	19	6,534	6,19	11,533	7	-4,533	-5,81	11,533			
	vfa hr	11,287	8	-3,287	-2,71	10,293	13	2,707	2,29	8,802	6	-2,802	-4,71	10,79			
	vfs hr	16,39	12	-4,39	-2,4	14,015	14	-0,015	-0,4	12,14	10	-2,14	-4,4	12,515			
	nart hr	103,118	112	8,882	13,64	97,1	103	5,9	4,64	94,091	86	-8,091	-12,36	94,091	94	-0,091	-4,36
	animals hr	18,645	6	-12,645	-9,57	14,902	9	-5,902	-6,57	11,947	13	1,053	-2,57	12,538			
	fas hr	44,915	35	-9,915	-2,95	36,346	46	9,654	8,05	29,581	23	-6,581	-14,95	30,934			
	stroop3 hr	26,262	23,2	-3,062	-0,41	23,673	15,6	-8,073	-8,01	28,851	23	-5,851	-0,61		20,5		
	spotws hr	10,754	10	-0,754	0,54	9,222	12	2,778	2,54	8,456	8	-0,456	-1,46	8,456			
	speedcs hr	11,653	8	-3,653	-2,93	10,505	11	0,495	0,07	8,783	5	-3,783	-5,93	11,079			
	scolp hr	-1,917	2	3,917	0,54	-1,223	1	2,223	-0,46	-0,182	3	3,182	1,54	-1,57			
	ralvsix hr	5,608029957	8	2,391970043	-3,18302285	9,118936341	8	-1,11893634	-3,18302285	9,118936341	6	-3,11893634	-5,18302285				
	vr1 hr	35,10087964	37	1,899120365	1,156778202	32,45211375	38	5,54788625	2,156778202	35,10087964	30	-5,10087964	-5,8432218	33,40622675			
	vr2 hr	33,1002463	30	-3,1002463	-3,92736399	29,47364885	36	6,526351147	2,072636005	33,1002463	18	-15,1002463	-15,927364	30,82822234			

Appendix 2, Matrix 4.4. Evaluation of the linear predictors

		13				14												
		predicted	observed	obs-pre	obs-mean	predicted	observed	obs-pre	obs-mean									
	vff patient	8,115				13,475												
	vfa patients	5,776				11,167												
	vfs patients	8,169				17,869												
	nart pat	86,074	87	0,926	-9,56	115,546	113	-2,546	16,44									
	animals pat	9,613				20,613	7	-13,613	-5,26									
	fas patient	21,725				44,725												
	stroop3 p	35,955	29,1	-6,855	3,2	34,395	30,2	-4,195	4,3									
	spotws p	6,83	7	0,17	-2,46	14,422	15	0,578	5,54									
	speedcs p	7,043	4	-3,043	-4,78	9,863	12	2,137	3,22									
	scolp p	3,017	3	-0,017	2,42	-1,138	3	4,138	2,42									
	ralvsix p	6,316486365	6	-0,31648637	-3,03769882	8,473960113	7	-1,47396011	-2,03769882									
	vr1 p	31,01552239	24	-7,01552239	-10,5775318	38,30984292	37	-1,30984292	2,422468217									
	vr2 p	24,87156079	14	-10,8715608	-17,3765281	36,19377029	36	-0,19377029	4,623471895									
	CONTROL MEAN		SD		HIGH RISK MEAN		SD		PATIENT MEAN		SD							
	vff	13,73	3,99			12,81	4,76			9,74	3							
	vfa	11,44	3,55			10,71	4,12			7,35	3,16							
	vfs	15,35	4,32			14,4	4,66			11	3,67							
	nart	105,23	8,36			98,36	9,87			96,56	9,35							
	animals	17,97	6,31			15,57	4,58			12,26	3,84							
	fas	40,53	9,63			37,95	12,01			28,09	8,32							
	stroop3	21,31	5,08			23,61	5,54			25,9	5,01							
	spotws	11,03	2,25			9,46	2,44			9,46	2,91							
	speedcs	12,37	3,17			10,93	3,27			8,78	3,32							
	scolp	1,35	3,59			1,46	2,96			0,58	3,21							
	ralvsix	12,26336006				11,18302285				9,037698822								
	vr1	37,88218945				35,8432218				34,57753178								
	vr2	36,21812065				33,92736399				31,3765281								

Appendix 3. Appendix to Chapter seven; Handedness Questionnaire

HANDEDNESS QUESTIONAIRE

Research No:
Name:
Date Reviewed:
Date of Birth:

FAMILY HANDEDNESS

Age: Handedness			Age: Handedness		
Father:			Mother:		
Brothers:			Sisters		
Name: 1 . 2. 3. 4.			Name: 1. 2. 3. 4.		
Fathers side of family			Mothers family		
Grandfather			Grandfather		
Grandmother			Grandmother		
Uncles 1. 2. 3.			Uncles 1. 2. 3.		
Aunts 1. 2. 3.			Aunts 1. 2. 3.		

Adapted From The Edinburgh Handedness Inventory (Oldfield, 1971) and The Annett Handedness Questionnaire (Annett, 1970).

Handedness Examined By Demonstration (three trials) and verbal recall (one trial)

FIRST PRESENTATION	**Right**	**Left**	**Mixed**
1. Writing			
2. Drawing			
3. Throwing A Ball			
4. Scissors			
5. Toothbrush			
6. Knife (Without Fork)			
7. Spoon			
8. Broom (Upper Hand)			
9. Striking a Match (Match)			
10. Opening a Box (lid)			
11. Which foot do you kick with?			
12. Which eye is dominant (roll up piece of paper and give to them in both hands)			
13. Holding a racquet			
14. Hammering			
15. Holding thread to a needle			
16. Top hand holding a shovel			
17. Dealing cards			

SECOND PRESENTATION

3. Throwing A Ball
5. Toothbrush
9. Striking a Match (Match)
13. Holding a racquet
14. Hammering
17. Dealing cards
2. Drawing
6. Knife (Without Fork
10. Opening a Box (lid)
7. Spoon
8. Broom (Upper Hand)
15. Holding thread to a needle
1. Writing
16. Top hand holding a shovel
4. Scissors

THIRD PRESENTATION	**Right**	**Left**	**Mixed**
2. Drawing			
4. Scissors			
5. Toothbrush			
9. Striking A Match (Match)			
14. Hammering			
16. Top hand holding a shovel			
1. Writing			
8. Broom (Upper Hand)			
15. Holding thread to a needle			
6. Knife (Without fork)			
10. Opening A Box (Lid)			
17. Dealing Cards			
7. Spoon			
3. Throwing a Ball			
13. Holding a racquet			

Appendix 4. Appendix to Chapter nine

9.1 Calculation of quantitative genetic risk(Sham's method) for each of the high risk subjects

The example to be used is that case of a small family with an affected father, an unaffected mother, and a child at high risk. However the family trees of most of the high risk subjects were much more complex including many generations in some cases making some of the matrix computations complicated. The mathematical calculations were conducted in MATLAB, using a Sun Work Station. The matrices of genetic relatedness were compiled from the family trees by Gary Blackie.

Step one:

Write down a vector of predicted liabities (x).

To do this:

a). Set the prevalence:

The prevalence was estimated to be about 0.5% (see standard text book).

b). Calculate the threshold in Liability:

Given a prevalence of 0.5% the threshold in liability was calculated as the 99.5 percentile of the normal distribution (z= 2.58).

c). Calculate the expected liability for those above the threshold:

This is the value of the standard normal density function at the threshold divided by 0.005.

d). Calculate the expected liability for those below the threshold:

This is the value of the standard normal density function at the threshold divided by –0.955.

The threshold t such that P(z>t) 0.005 is 2.58 (from normal distribution). For the standard normal distribution the average value above a certain threshold is simply the value of the density function about the threshold, divided by the probability above the threshold. The value of the density function at threshold t is

[1/square root (2*pi)]* exponential ($-t^2/2$).

The probability above t is the prevalence or 0.005 (because this is how t is set in the first place). So the average value of liability above the threshold is the result of the formula above, the value of the density function at the threshold (0.014), divided by the probability above the threshold (0.005), giving an average liability above the threshold of 2.85.

Similarly the average value of liability below the threshold is the same value,

[1/square root (2*pi)]* exponential ($-t^2/2$),

except to get the average liability below the threshold, the value of the density function at the threshold (0.014) is divided by the prevalence -1, (0.005 –1; the probability below the threshold). The average value of liability below the threshold is calculated as –0.14. This means that the value of x for those who are affected will always be 2.85, and for those who are unaffected, -0.14. Therefore the vector of predicted liabilities x will be;

2.86 (father affected)
-0.14 (mother unaffected)
-0.14 (child unaffected)

Step two:

Write down the correlation matrix between genetic loadings, R.

Spousal correlation will be 0, and parent-child correlation will be 0.05, 1 is correlation with self. So that R is:

1	0	0.5
0	1	0.5
0.5	0.5	1

(matrix interpreted from left to right;

Row 1:father/father correlation (r), father/mother r, father/child r

Row 2:mother/father r, mother/mother r, mother/child r

Row 3:child/father r, child/mother r, child/child r).

Step three

Write down a correlation matrix between liabilities, V.

1 for the diagonal, (h^2)*R for the off diagonals (h^2 is heritability squared, and is estimated to be approximately 70% giving h^2 the value of 0.7.

1	0	0.7*0.5
0	1	0.35
0.35	0.35	1

Step four

The expected genetic loading g, given the liabilities x can now be calculated by the formula (V^{-1}) x.

Appendix 5. Papers describing the data presented in this thesis

The following papers were outlined in the section 'summary and organisation of the thesis'.

Psychological Medicine, 1999, **29**, 1161–1173. Printed in the United Kingdom

Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS)

M. BYRNE,[1] A. HODGES, E. GRANT, D. C. OWENS AND E. C. JOHNSTONE

From the Department of Psychiatry, University of Edinburgh

ABSTRACT

Background. Finding risk indicators for schizophrenia among groups of individuals at high genetic risk for the disorder, has been the driving force of the high risk paradigm. The current study describes the preliminary results of a neuropsychological assessment battery conducted on the first 50% of subjects from the Edinburgh High Risk Study.

Methods. One hundred and four high risk subjects and 33 normal controls, age and sex matched, were given a neuropsychological assessment battery. The areas of function assessed and reported here include intellectual function, executive function, perceptual motor speed, mental control/encoding, verbal ability and language, learning and memory measures, and handedness.

Results. The high risk subjects performed significantly more poorly than the control subjects in the following domains of neuropsychological function: intellectual function, executive function, mental control/encoding and learning, and memory. Controlling for IQ, high risk subjects made significantly more errors on the Hayling Sentence Completion Test (HSCT), took longer to complete section A of the HSCT, had lower scores on the delayed recall condition of the visual reproductions subtest of the Wechsler Memory Scale-Revised, and had significantly poorer Rivermead Behavioural Memory Test (RBMT) standardized scores. The presence of significant group by IQ interactions for the RBMT and time to complete section A of the HSCT suggested that differences among the groups were more marked in the lower IQ range. Performance on the HSCT was found to be related to the degree of family history of schizophrenia.

Conclusions. High risk subjects performed more poorly than controls on all tests of intellectual function and on aspects of executive function and memory.

INTRODUCTION

Schizophrenia is widely accepted to be a disorder of the brain (Weinberger, 1995). There are few certainties about the aetiology of the disorder, but a familial background and presumably genetic liability is certain to be important (Gottesman & Shields, 1976, 1982). Exactly what is inherited is the subject of much debate. There is evidence, from retrospective studies, to suggest that individuals who later develop schizophrenia display disturbances of motor development in infancy (Fish *et al.* 1992; Walker *et al.* 1993, 1994), and prospective studies show that they have language problems (Jones *et al.* 1994), and behavioural difficulties (Done *et al.* 1994) as children, suggesting the presence, however subtle, of continuous neurological deficit throughout childhood. If what is inherited is the propensity for the development of schizophrenia, as the balance of current evidence suggests, vulnerability markers in biological

[1] Address for correspondence: Ms Majella Byrne, University Department of Psychiatry, University of Edinburgh, Kennedy Tower, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF.

relatives of patients maybe very useful in identifying those at heightened risk for the disorder. Finding risk indicators for schizophrenia has been an endeavour of the high risk studies and studies of adult relatives of schizophrenic patients. High risk, in this context refers to the study of individuals who are considered to have a higher statistical risk of developing schizophrenia than members of the general population. Risk in this project, is based on genetic relatedness. The high risk paradigm typically involves the recruitment of children of patients with schizophrenia, with assessment at entry to the study and a long period of follow-up in a bid to closely identify the factors that lead to the development of schizophrenia in adult life (Asarnow, 1988; Cornblatt & Obuchowski, 1997 – for review and commentaries of high risk research). A difficulty with the high risk paradigm is that the follow-up period is often as much as 20 years and such studies have suffered greatly from high rates of attrition. Studies of the biological relatives of patients with schizophrenia usually involve a single assessment conducted in an attempt to measure the prevalence of deficits and possible markers in such populations.

It is well established that the diagnosis of schizophrenia is often accompanied by neuropsychological impairments (Bilder, 1996), specifically impairments of attention, memory, abstraction and mental flexibility or 'executive function' (Elliott & Sahakian, 1995; Elliott *et al.* 1995; Gur *et al.* 1997). A recent review of the evidence for neurocognitive deficits in schizophrenia based on 204 studies (Heinrichs & Zakzanis, 1998) concluded that schizophrenia is characterized by a broadly based cognitive impairment with differing degrees of impairment in many domains as measured on standard clinical tests. The role these impairments play in the pathogenesis of the disorder is less clear, whether they are an integral part of the illness or are a secondary effect of the other features remains uncertain. It has been difficult to find consistent correlations between demonstrated neuropsychological impairment and structural brain changes. It is well established that brain structure in groups of schizophrenic patients differs from that of groups of normal controls. Classical approaches have led to the suggestion that cognitive deficits in schizophrenia implicate dysfunction in frontal, temporal, limbic or integrated frontotemporal and frontolimbic systems (Bilder, 1996).

Neuropsychological dysfunction has been reported in relatives of schizophrenia patients (e.g. Faraone *et al.* 1995; Toomey *et al.* 1998). Specific domains of neuropsychological dysfunction have been identified. Areas that have been found to be impaired in relatives include sustained attention, perceptual motor speed, concept formation and abstraction/executive function, and mental control-encoding. Other deficits suggested are verbal fluency, verbal learning and memory (Faraone *et al.* 1995). The area of attention has been the focus of much research in high risk studies and in studies of adult relatives of schizophrenia patients. The present study aims to present the preliminary findings of the neuropsychological assessment of a group of young people at high genetic risk for the development of schizophrenia. The test battery chosen was designed to include tests which have been previously shown to differentiate subjects at high risk for schizophrenia and controls (Kremen *et al.* 1994), tests that have shown differences between schizophrenic patients and controls, and tests that localize to parts of the brain that have been shown on imaging or other investigations to differ between schizophrenia patients and controls. The battery was designed to be repeatable and not so prolonged that compliance would be reduced. These are the preliminary findings of an ongoing study.

Background to the Edinburgh High Risk Study

The Edinburgh High Risk Study (EHRS) was set up in 1994. The study was designed to follow young adults through an estimated 60% of their maximum risk period for developing schizophrenia, and over a 5-year period. This design redresses some of the difficulties of other high risk projects (Erlenmeyer-Kimling & Cornblatt, 1987). Recruitment in young adulthood prevents such high attrition rates from childhood to adulthood. The onset of schizophrenia most commonly occurs within this age group (Häfner & An Der Heiden, 1997). The change from risk and prodromal state to florid illness is not clearly understood, opportunities to study it have been few, however, it can be closely monitored in this investigation. It has the

advantage of being a study of adult relatives of patients with schizophrenia as well as being a high risk design. Differences between functional and behavioural patterns in childhood and adulthood preclude the generalization of findings in children to adults. This is avoided in the EHRS.

The sample under study comprises young persons aged between 16 and 25 years who have been identified to have at least two close members of their family suffering from schizophrenia, increasing their individual genetic risk for the disorder. It was intended that the study should concern 200 well young people from families where two or more people are affected by schizophrenia, (some from high density families, families that have multiple affected members), 30 normal controls without a family history of psychotic illness in either first- or second-degree relatives and 30 sporadic cases of schizophrenia. The groups are being followed up at 18 month intervals for 5 years. At each assessment subjects receive a detailed clinical assessment described in detail elsewhere (Hodges *et al.* 1999), structural brain imaging in the form of MRI scans (Lawrie *et al.* 1999) and detailed neuropsychological assessment, described here.

The overall aims of the study include the determination of the clinical, psychological, and neurological features, and detailed brain structures that distinguish those members of high risk families who develop schizophrenia from those who will not. We also seek to compare the results from these groups with other cases of first-episode schizophrenia and normal controls. The purpose of this paper is to describe the results of a neuropsychological assessment of the first 50% of the identified sample, at high genetic risk for schizophrenia, compared with normal controls.

METHOD

Subjects

This report does not consider the results of the neuropsychological assessments of the first-episode patients. Data collection is incomplete for the first episode patients to date due to difficulties in assessment of patients who are acutely psychotic. One hundred and four subjects (mean age 21·1 (S.D. 2·3), 51% male) were recruited from families where at least two close relatives of the subject were affected by schizophrenia. They were compared to 33 normal controls (mean age 21·2 (S.D. 2·8), 55% male), matched as closely as possible for age, sex and social class based on fathers occupation, who had no relatives with any psychotic disorder apart from dementia in old age. Details of the recruitment of the groups is outlined in Hodges *et al.* 1999. The demographic characteristics of the groups, including, age, sex, distribution of social class at birth and educational attainment are presented in Table 1. Social class at birth was based on father's occupation and information was collected from birth registrations. Social class was considered unclassifiable if there was no means of knowing the father's occupation at birth of the subject, or if the father was employed by the armed forces and the rank was unknown.

Neuropsychological assessment battery

A battery of neuropsychological assessments was administered to each individual. The tests were organized according to neuropsychological functions on the basis of general neuropsychological practice (Lezak, 1995), and in a manner similar to previous studies of adult relatives of patients with schizophrenia (Kremen *et al.* 1992, 1994). The tests administered and functions they serve to examine are outlined in Table 2. Most of the tests (1, 2, 4–8, 10–16) are well described elsewhere (Lezak, 1995; Spreen & Strauss, 1991). The Hayling Sentence Completion Test (HSCT, Burgess & Shallice, 1996) is a relatively new test. It is composed of two conditions, in both the sentence must be completed as quickly as possible with a one word answer. In the first condition, subjects are required to finish a sentence by inserting a word that sensibly completes the sentence. In the second condition subjects are required to give a ridiculous ending to the sentence by inserting a word that makes no sense in the context of the sentence (incongruous condition). The errors are scored according to the degree of sense made by the sentence completion. Category A errors are scored if a sentence in the incongruous condition is correctly completed. Category B errors are scored if the sentence makes some sense e.g. 'The whole town came to hear the Mayor……, answer: Sing.' Raw scores are then converted to scaled scores. Overall error scores were examined here. There are many

Table 1. *Sociodemographic characteristics of the group*

	Controls (N = 33)		High risk (N = 104)		Test statistic	P
Age, mean (S.D.)	21·17	(2·25)	21·14	(2·83)	t = 0·06*	0·95
Gender, N (%)						
Male	17	(51·4)	57	(54·8)	χ^2 = 0·11†	0·74
Female	16	(48·5)	47	(45·2)		
Social class at birth (fathers occupation), N (%)						
I and II	10	(30·3)	25	(24·0)		
III	16	(48·5)	52	(50·0)	χ^2 = 1·02†	0·80
IV and V	4	(12·1)	19	(18·3)		
Unclassifiable	4	(9·1)	8	(7·7)		
Educational attainment N (%)						
Left school before 16 years	2	(6·1)	9	(8·7)		
Still at school	2	(6·1)	5	(4·8)		
GCSEs only	2	(12·1)	38	(36·5)	χ^2 = 2·45‡	0·01
Highers only	4	(24·2)	14	(13·5)		
Certificate/diploma	8	(6·1)	16	(15·4)		
Entered university	2	(45.5)	22	(21.2)		
	15					

*Independent samples t test, two-tailed; †Pearson's chi-square statistic; ‡Mann–Whitney U test.

Table 2. *Neuropsychological assessment battery*

Neuropsychological function	Tests
Current intellectual function	(1) Wechsler Adult Intelligence Scale Revised (WAIS-R; Wechsler, 1981)
Pre-morbid intellectual function	(2) National Adult Reading Test (Nelson & O'Connell, 1978; Nelson, 1982)
Executive function	(3) Hayling Sentence Completion Test (Burgess & Shallice, 1996) (4) Stroop Colour Word Test (computerized translation of Golden, 1978) (5) Verbal Fluency (FAS) and Semantic category, animals (Spreen & Strauss, 1991)
Perceptual motor speed	(6) WAIS-R Digit-symbol age scaled scores
Mental control/encoding	(7) WAIS-R Digit span age scaled scores (8) WAIS-R Arithmetic age scaled scores
Sustained attention	(9) Continuous Performance Test – Identical Pairs Version (CPT–IP) (Cornblatt *et al.* 1988)
Verbal ability and language	(10) Token test (Spreen & Benton, 1969, 1977) (11) WAIS-R Vocabulary age scaled scores
Learning and memory	
General memory	(12) Rivermead Behavioural Memory Test (Wilson *et al.* 1985)
Verbal learning	(13) Rey Auditory Verbal Learning Test (Rey, 1964)
Visual memory	(14) Wechsler Memory Scale – Revised, Visual Reproductions, immediate and delayed conditions (Wechsler, 1987)
Verbal memory	(15) Rivermead Behavioural Memory Test Story, immediate and delayed conditions (Wilson *et al.* 1985)
Handedness	(16) Annett Handedness Scale (Annett, 1970) and the Edinburgh Handedness Inventory (Oldfield, 1971)

variants of the continuous performance test which have been used extensively to evaluate the role of sustained attention in schizophrenia. The Continuous Performance Test – Identical Pairs (CPT–IP) version (Cornblatt *et al.* 1988) was used here and is a cognitively challenging form of the task. In high risk research more difficult forms of the CPT have provided evidence to suggest that attentional deficits may be markers for a genetic liability to schizophrenia (Rutschmann *et al.* 1977; Nuechterlein, 1983; Cornblatt & Erlenmeyer-Kimling, 1985). The

CPT–IP takes the form of presenting a series of numbers and shapes (in separate conditions), to test both visual and spatial processing capabilities. Subjects were required to respond whenever two identical stimuli appeared in a row. The CPT–IP is well described elsewhere (Cornblatt *et al.* 1988). First, numbers were presented without any distraction, the stimulus appeared on the screen for 50 ms followed by a dark screen for 950 ms. The numbers condition was followed by the shapes condition, presented in an identical manner. The purpose of these two conditions was to assess if there was a deficit in sustained attention. Next, numbers and shapes were again presented at the same rate, this time in the presence of both visual and auditory distractions. The purpose of these conditions was to assess for evidence of abnormal distractibility. In all conditions there were 30 target trials, 30 close but not exact matches termed 'colds', and 90 random unrelated stimuli called 'filler' trials. Three performance measures of the CPT–IP were analysed. These included two signal detection indices, d′, to measure declines in sensitivity and attentional capacity, β, to measure shifts in response style or tendency to over respond *versus* under respond, converted to the natural log scale ($\ln\beta$) and also random errors on the task converted to the natural log scale (ln randoms) (Cornblatt *et al.* 1988). All performance measures were calculated by the CPT-IP software.

Statistical analyses

Given that gender differences have been demonstrated in cognitive function in patients with schizophrenia (Lewine *et al.* 1997) and in relatives (Kremen *et al.* 1997) of such patients, a gender by group (whether high risk or control) analysis of variance (ANOVA) was conducted for the individual test scores. Analyses were conducted separately for males and females where group by gender interactions were found. An inequality between the groups in terms of IQ was revealed in the initial analysis. Given the likely effect of IQ on neuropsychological test results, an analysis of covariance (ANCOVA) was performed with WAIS-R Full Scale IQ as a covariate wherever a main effect for group was found in the initial analysis. The purpose was to identify whether the group differences suggested in certain domains of function, were independent of IQ. All ANCOVAs were performed using the General Linear Model option of SPSS 7.5 for Windows (SPSS, 1996). The ANCOVA model, included group (whether high risk or control) as a factor, with Full Scale IQ as the covariate, and a group × IQ interaction term. For data that was not normally distributed ANCOVAs were conducted on the ranked dependent variable and the ranked covariate (Conover & Iman, 1982), with a group × IQ interaction term also included in the model. For the continuous performance test the research questions 'Is there a difference between the groups on measures of sustained attention?' and 'Is there a difference between the groups in terms of distractibility?' were answered by submitting the three performance measures, d′, $\ln\beta$ and ln randoms to a 2 (group; high risk *versus* control) by 2 (distraction; no-distraction *versus* distraction) by 2 (stimulus; numbers *versus* shapes) repeated measures ANCOVA with WAIS-R Full Scale IQ as a covariate. The summary statistics presented in the tables take the form of means and standard deviations for normally distributed data, medians with the 25th and 75th percentiles for the non-normal data. In the case of the HSCT times on section A, the data were transformed to normal using a log transformation, the geometric mean and the 95% confidence interval calculated on the log scores and converted back to the original scale is presented (Altman *et al.* 1983). Non-parametric analyses were conducted where the scores were categorical or were not normally distributed and suitable transformations to normality could not be found. All analyses were conducted using SPSS 7.5 for Windows (SPSS, 1996).

RESULTS

The results are organized by domain of function, the results of the initial analyses are displayed in Table 3 and the results of the CPT–IP are displayed in Table 5.

Intellectual function

High risk (HR) subjects demonstrated significantly lower scores on all measures of current intellectual and pre-morbid intellectual function. HR subjects had a significantly ($P = 0{\cdot}01$) lower mean verbal IQ, mean performance IQ ($P = 0{\cdot}01$) and mean full scale IQ ($P = 0{\cdot}05$) com-

Table 3. *Comparison of neuropsychological functioning in controls and high risk*

	Controls (N = 33) Mean (S.D)	High risk (N = 104) Mean (S.D.)	Main effects of group	
			F	P
Current intellectual function				
Verbal IQ	102·54 (12·68)	97·77 (11·82)	4·05	0·05
Performance IQ	107·48 (16·09)	99·78 (14·26)	7·05	0·01
Full Scale IQ	105·15 (14·22)	98·48 (13·05)	6·47	0·01
Pre-morbid intellectual function				
National Adult Reading Test – Full Scale IQ	104·88 (8·22)	98·69 (10·01)	9·72	0·002
Executive function				
Stroop colour word test, interference condition	21·42 (5·12)	23·24 (5·19)	2·97	0·09
Verbal fluency				
FAS	40·18 (9·56)	38·69 (12·74)	0·39	0·53
Semantic category animals	17·94 (6·41)	16·08 (4·77)	3·32	0·07
Hayling response times on section A*	14·36 (12·57, 16.46)	18·45 (16·60, 20·60)	5·04	0·03
Hayling Error Score†	3·00 (0·5, 5·00)	5·00 (1, 18·25)	z = 2·46	0·01
Perceptual motor speed				
WAIS-R digit symbol age scaled scores	11·27 (2·75)	10·19 (2·84)	3·32	0·07
Mental control/encoding				
WAIS-R digit span forward age scaled scores	8·21 (2·29)	8·50 (2·18)	0·46	0·50
WAIS-R digit span backward age scaled scores	7·76 (2·33)	7·18 (2·33)	1·67	0·20
WAIS-R arithmetic age scaled scores	10·12 (3·02)	9·37 (2·45)	2·04	0·16
WAIS-R arithmetic‡				
Males	11·47 (2·76)	9·51 (2·61)	7·19	0·01
Females	8·69 (2·65)	9·21 (2·24)	0·60	0·44
Verbal ability and language				
WAIS-R Vocabulary age scaled scores	9·30 (1·85)	8·51 (2·36)	3·00	0·09
Token test (overall total)†	163·00 (162, 163)	163·00 (161, 163)	z = 1·70	0·09
Learning and memory				
RAVLT				
Total of conditions 1–5	54·73 (8·49)	50·85 (8·81)	4·50	0·04
Delayed recall	11·79 (2·55)	10·20 (2·81)	7·94	0·01
WMS-R Visual reproductions				
Total immediate recall	37·40 (2·79)	35·72 (4·12)	3·62	0·06
Total delayed recall	35·40 (4·55)	32·85 (5·96)	3·88	0·05
Rivermead Behavioural Memory Test				
Standardized score†	22·00 (21·5, 24)	22·00 (20, 24)	z = −1·97	0·05
Asymmetry: Handedness				
Right-handed	N = 30 (91%)	N = 92 (88·5%)	χ^2 = 0·15	0·69
Left-handed	N = 3 (9%)	N = 12 (11·5%)		

* Analysis conducted on the natural log of response times for section A, geometric mean times presented here, with 95% CI for the mean calculated on the log scale and converted back to the original.

† Data not normally distributed and analysed using non-parametric Mann–Whitney U test, medians (25th and 75th percentiles) presented.

‡ Group by gender interaction, analysis conducted separately for males and females.

pared with the control subjects. HR subjects had significantly (P = 0·002) lower mean NART full scale IQ estimates compared to controls.

Executive function

There was a trend (P = 0·09) for controls to achieve faster times in the interference condition of the Stroop test compared with the HR subjects. There was no significant difference between the groups in terms of verbal fluency, as measured by the FAS test. There was a trend (P = 0·07) for controls to produce the names of more four-legged animals than HR subjects. HR subjects were poorer than controls on measures of the Hayling Sentence Completion Test (HSCT). As the error scores were not normally distributed the initial analysis was performed using non-parametric methods, the median error score (25th and 75th percentiles) is presented in Table 3. High risk subjects made significantly (P = 0·01) more errors than controls. The time in seconds to sentence completion in section A of the HSCT was transformed to a normal distribution using a natural log transformation.

Table 4. *Analysis of covariance investigating the effect of full scale IQ on neuropsychological test performance, where initial analysis revealed significant* ($P \leqslant 0{\cdot}05$) *group differences*

	Main effect for group		Main effect of covariate full scale IQ		Group, full scale IQ interaction	
	F	*P*	*F*	*P*	*F*	*P*
Executive function						
Hayling response times on section A*	5·06	0·03	1·40	0·24	4·13	0·04‡
Hayling error score†	5·09	0·03	3·68	0·06	2·48	0·12
Learning and memory						
RAVLT						
Total of conditions 1 to 5	0·39	0·53	33·55	< 0·001	0·23	0·63
Delayed recall	1·24	0·27	14·35	< 0·001	0·71	0·40
WMS-R						
Visual reproductions	3·75	0·05	36·18	< 0·001	3·37	0·07
Total delayed recall						
Rivermead Behavioural Memory Test standardized score†	6·36	0·01	9·29	0·003	5·08	0·03§

* Analysis conducted on the natural log of response times for section A, geometric mean times presented here, with 95% CI for the mean calculated on the log scale and converted back to the original.

† Data not normally distributed and analysed using non-parametric Mann–Whitney *U* test, medians (25th and 75th percentiles) presented.

‡ See Fig. 1.

§ See Fig. 2.

The results (see Table 3) suggest that the HR subjects were significantly ($P = 0{\cdot}03$) slower than controls on this task (the geometric mean with a 95% CI calculated on the log scores and converted back to the original scale are presented here.

Perceptual motor speed

There was a trend ($P = 0{\cdot}07$) for HR subjects to achieve lower digit symbol scaled scores than controls (see Table 3).

Mental control/encoding

There were no differences between HR subjects and controls in terms of WAIS-R digit span forwards or backwards. There was no overall group effect for WAIS-R arithmetic scaled scores. Due to the presence of a group by sex interaction for arithmetic analysis was conducted separately for males and females. The results revealed that male HR subjects achieved significantly lower ($P = 0{\cdot}01$) arithmetic scores than male controls. There was no significant difference for females.

Verbal ability and language

There was a trend ($P = 0{\cdot}09$) towards lower mean WAIS-R vocabulary scores for HR subjects compared to controls. There was also a trend ($P = 0{\cdot}09$) for HR subjects to achieve poorer scores on the Token Test compared with controls.

Learning and memory

HR subjects performed more poorly than controls on all measures of learning and memory. HR subjects learned and remembered significantly ($P = 0{\cdot}04$) fewer words across all five trials of the RAVLT than controls. They remembered significantly ($P = 0{\cdot}01$) less words on the delayed recall section of the RAVLT. There was a trend ($P = 0{\cdot}06$) towards poorer scores among the HR subjects compared with the controls on the visual reproductions subscale of the WMS-R for the immediate condition and HR subjects performed significantly ($P = 0{\cdot}05$) worse on the delayed recall section of this task. The HR subjects had significantly ($P = 0{\cdot}05$) lower standardized scores on the RBMT compared with controls, the median (25th and 75th percentiles) is presented in Table 3.

Handedness

There was no difference between the groups in terms of hand preference classified here as preferred hand for writing.

The results of the analysis of covariance are presented in Table 4. Controlling for IQ a significant main effect for group was noted (with no group by IQ interaction) for HSCT error scores ($P = 0{\cdot}03$) and the delayed recall condition of the WMS-R visual reproductions ($P = 0{\cdot}05$), where the performance of the high risk

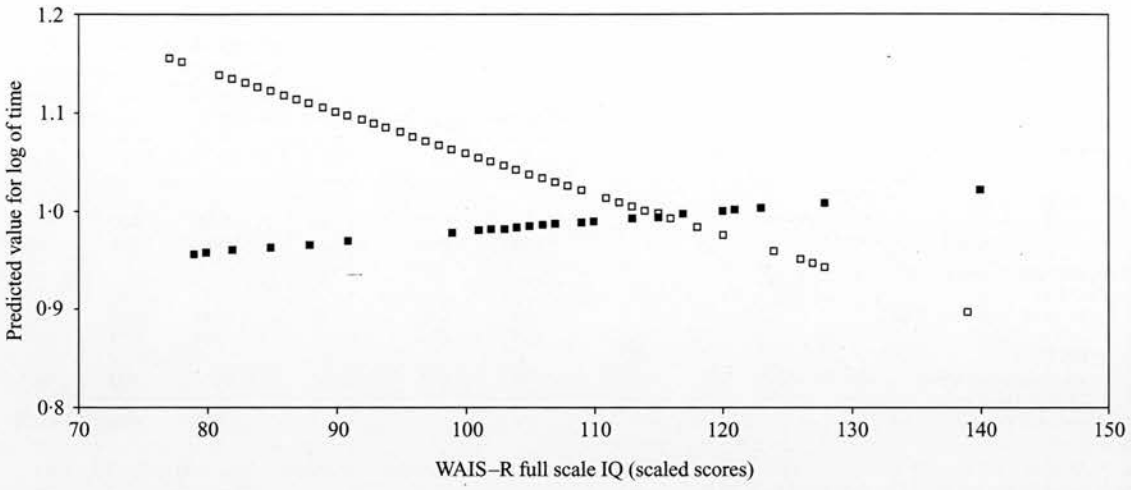


FIG. 1. Scatter plot of predicted values for the log transformed time values for the Hayling Sentence Completion Test, section A (□, high risk; ■, control).

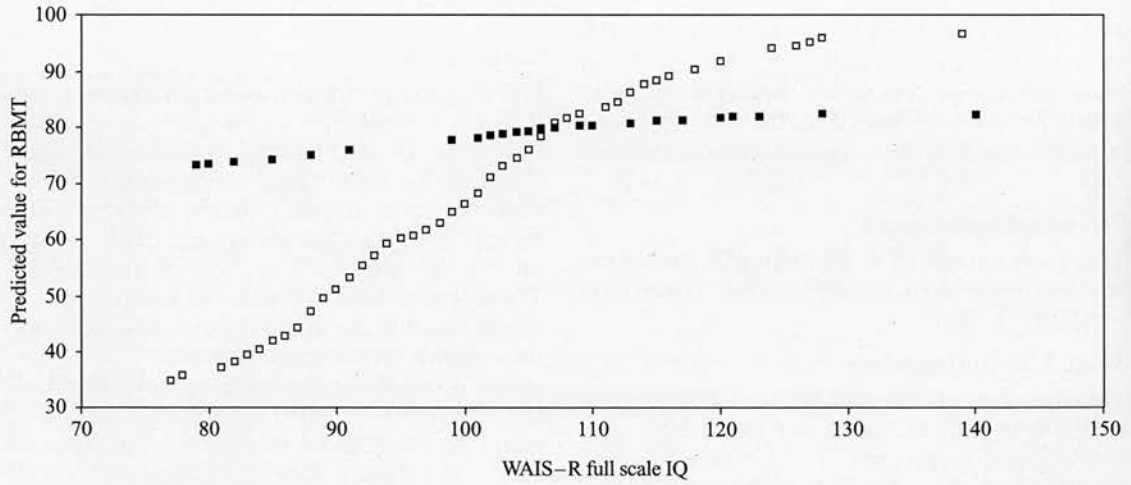


FIG. 2. Scatter plot of predicted values for the ranked standardized scores of the Rivermead Behavioural Memory Test (□, high risk; ■, control).

group was poorer than that of the control group on these tasks. A significant main effect for group was found for the Rivermead Behavioural Memory Test standardized scores ($P = 0{\cdot}01$) and for the response times for HSCT section A ($P = 0{\cdot}03$), with the high risk group performing more poorly than the control group, however, significant group by IQ interactions were found making the interpretation of the main effect less clear. The interactions are graphically presented in Figs. 1 and 2. A scatter plot of the predicted values from the ANCOVA model for the log-transformed time values for section A of the HSCT, plotted against WAIS-R Full Scale IQ is presented in Fig. 1. In Fig. 2 the predicted values for the ranked standardized scores of the RBMT were plotted against WAIS-R Full Scale IQ. The residuals from both models were normally distributed. The model predicted the HR group to perform more poorly than the control subjects on the RBMT in the lower range of IQ but better than the control group when IQ increased beyond 110. A similar result was found for the HSCT, time on section A, where the HR group

Table 5. *Summary statistics for the Continuous Performance Test–Identical Pairs version*

	Controls Mean (S.D.)	High risk Mean (S.D.)	Group effect controlling for IQ* F	P
d′				
Numbers				
Fast no distraction	1·96 (0·88)	1·83 (0·84)		
Fast distraction	1·67 (0·78)	1·70 (0·91)		
Shapes			0·29	0·59
Fast no distraction	1·93 (0·58)	1·70 (0·71)		
Fast distraction	2·29 (0·79)	1·93 (1·80)		
Log beta				
Numbers				
Fast no distraction	−0·37 (0·77)	−0·30 (0·72)		
Fast distraction	−0·04 (0·54)	−0·01 (0·73)		
Shapes			0·04	0·85
Fast no distraction	−0·14 (0·63)	−0·23 (0·74)		
Fast distraction	−0·23 (0·96)	−0·20 (0·80)		
Log randoms				
Numbers				
Fast no distraction	0·19 (0·40)	0·48 (0·63)		
Fast distraction	0·40 (0·51)	0·61 (0·60)		
Shapes			0·83	0·36
Fast no distraction	0·37 (0·51)	0·50 (0·64)		
Fast distraction	0·35 (0·49)	0·55 (0·73)		

* The F and P values come from a 2 Group (High risk *versus* Control) × 2 Stimulus (Shapes or Numbers) × 2 Distraction (distraction *versus* no distraction) analysis of covariance with WAIS-R full scale IQ as a covariate. There were consistent and significant effects of IQ for d′ and ln randoms but not for ln beta. There were no two-way interactions involving groups.

Table 6. *Neuropsychological assessment results: analysis by family history*

	Absent (N = 33)	Second degree (N = 29)	First and second degree (N = 63)	More than one first degree (N = 10)	F/χ^2	P
Executive function						
HSCT response times to section A*	14·36 (12·57–16·46)	20·79 (16·62–26·59)	17·42 (15·37–20·43)	16·01 (12·96–19·95)	2·45†	0·09
HSCT total error Score‡	3·00 (0·5, 5·00)	4·00 (1·00, 11·00)	5·00 (1·00, 19·00)	14·50 (4·75, 21·50)	9·61§	0·02
Memory tests						
RBMT standardized score§	22·00 (21·00, 24·00)	22·00 (20·00, 20·00)	22·00 (20·00, 24·00)	21·50 (18·75, 23·25)	4·99§	0·17
WMS-R Visual Reproductions delayed recall, Mean (S.D.)	35·40 (4·55)	34·11 (5·11)	32·17 (6·28)	33·44 (6·23)	2·29†	0·08
Full scale IQ, Mean (S.D.)	105·15 (14·22)	100·37 (11·05)	97·94 (13·84)	96·30 (14·01)	2·39†	0·07

* Analysis conducted on the natural log of response times for section A, geometric mean times presented here, with 95% CI for the mean calculated on the log scale and converted back to the original.
† Parametric oneway ANOVA.
‡ Medians (25th and 75th percentiles) presented.
§ Kruskall–Wallis oneway ANOVA.

were predicted to take longer than controls to complete the task when IQ was in the lower range but the opposite was true when IQ increased above 116.

The results of the CPT–IP are presented in Table 5. We did not find any main effect for group for any of the performance indices (Table 5). There were no two-way interactions involving group, suggesting that there were no differences between the high risk and control group on any of the performance measures of the CPT–IP measuring sustained attention or distractibility. There were consistent and significant effects of IQ for d′, and ln randoms but not for ln β.

The degree to which measures of the Hayling Sentence Completion Test, the RBMT and the WMS-R visual reproductions delayed recall condition were related to family history of

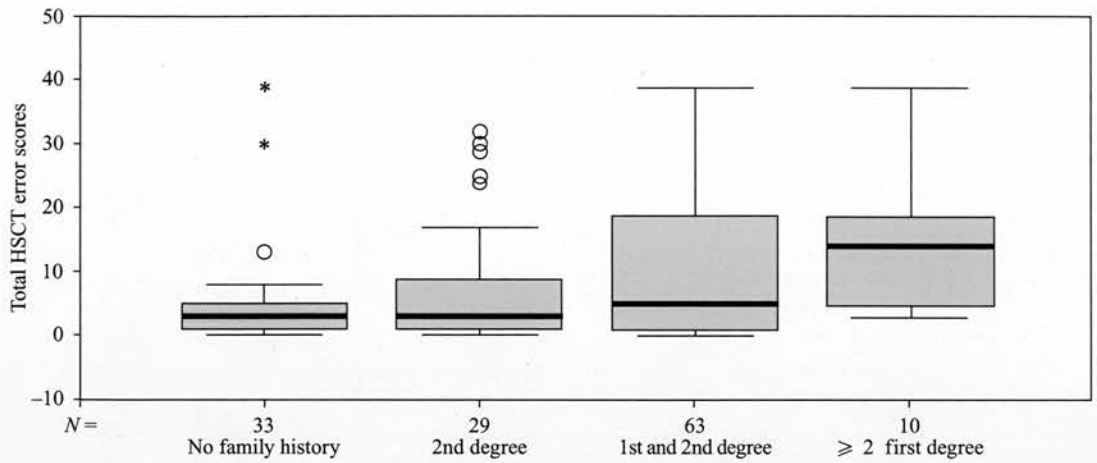


FIG. 3. Profile of HSCT error scores by family history groupings (○, an outliers – defined as a case with values between 1·5 and 3 box-lengths from the upper or lower edge of the box; *, an extreme value – defined as a case with a value > 3 box-lengths from the upper or lower edge of the box (see SPSS, 1996)).

schizophrenia, was investigated (given that the results of these tests seem to be related to subject status, whether HR subject or control). For the purposes of this analysis, degree of family history for schizophrenia was defined as: no family history (controls); at least two second-degree relatives affected; one first-degree relative and at least one other second-degree relative affected; at least two first-degree relatives affected. There was a non-significant trend ($P = 0{\cdot}07$) towards a difference across family history groups in terms of full scale IQ. The analysis involving family history groups was, therefore, not stratified by IQ as the difference was not significant. The results are described in Table 6.

There was a relationship between family history and Hayling error scores (Fig. 3), with those with two or more first-degree relatives performing significantly more poorly than the other groups and all groups performing worse than controls in terms of overall errors ($P = 0{\cdot}02$). There were no significant differences for any other measures.

DISCUSSION

The results to date show that for many of the neuropsychological assessments there was at least a trend towards poorer performance among the HR group compared to the controls (Table 3). Preliminary results of a battery of neuropsychological assessments are presented here for a relatively small but highly specialized, and we feel, very important sample. We were interested in investigating the possible presence of neuropsychological deficits among the HR group compared to the controls in a number of domains of function as outlined in Table 2. Finding significantly lower group performances among HR group (which is probably heterogeneous) compared with the controls in any domain of function is important as it hints at possible areas of vulnerability that may be especially marked in some subgroups. Neuropsychological deficits in this young well population were expected to be subtle, otherwise such individuals would be presenting for treatment of clinically relevant impairments, which would be disruptive to vocational and social functioning. It is for the above reasons that correction of multiple comparisons have not been made. Many areas of functioning were tested, but each was decided *a priori*. We were interested in assessing all domains individually and not the general null hypothesis (Perneger, 1998). Our results agree with the findings of previous HR research and indicate vulnerability in areas implicated in schizophrenia, namely executive function, memory and general intellectual performance.

The most striking finding was the general intellectual disadvantage of the HR group

compared with the control group, as evidenced on all measures of intellectual functioning. This discrepancy in IQ between the groups explained some of the differences found on the other neuropsychological tests. Controlling for IQ and IQ by group interactions, group differences remained for the HSCT error scores, time to complete section A of this test, delayed recall of the visual reproduction subtest of the WMS-R and the RBMT standardized scores (Table 4). The initial group differences found for the RAVLT were overwhelmingly accounted for by the differences in IQ among the groups, suggesting that performance on this test of verbal memory and learning is positively related to intellectual capability and not related to genetic risk for schizophrenia. There have been previous reports of lower IQ in childhood among those at risk for schizophrenia compared with controls (e.g. Offord & Cross, 1971; Neale, 1984) and this finding has been interpreted as the possible presence of minimal brain damage in the pre-schizophrenic group (Offord & Cross, 1971). Jones *et al.* (1994) found that low educational test scores at ages 8, 11 and 15 were risk factors for the later development of schizophrenia and were not explained by social class. Results from the New York High Risk project suggested that those at high risk for schizophrenia had lower IQ scores at ages 7 and 9 compared with subjects at high risk for affective disorders (Ott *et al.* 1997). The finding of reduced IQ scores in the HR group compared to a control group is not new and confirms previous reports. The group by IQ interactions for the RBMT standardized scores and the HSCT times to complete section A, make the interpretation of the main effect for group difficult. The predicted values from the models with significant group by IQ interactions, plotted against Full Scale IQ, are presented in Fig. 1 for time on section A of the HSCT and in Fig. 2 for the RBMT standardized scores. Both scatter plots show that the greatest predicted differences between the groups exists in the lower IQ range, suggesting that IQ may be a modifying variable in the relationship between group and these neuropsychological measures. Previous studies have suggested that having a lower IQ may be a risk factor for the development of schizophrenia (e.g. Ott *et al.* 1997; Erlenmeyer-Kimling *et al.* 1984; Jones *et al.* 1994). It does not appear to be a lower IQ *per se* that is the problem as the controls within the lower IQ range do not show the same disadvantage on the RBMT, or on the time to complete the HSCT section A. From Figs. 1 and 2 it can be seen that the slope of the line for the predicted values for the controls is slight compared with the slope for the HR group. Also, HR subjects with higher IQs had predicted values greater than the controls on these measures, although the magnitude of the differences was not so marked. This may indicate that having a higher IQ is somewhat protective against impairment in these domains of function in the HR group. While there was no significant group by IQ interaction for the HSCT error scores the profile of the plotted predicted values are very similar with the largest differences between the HR and control groups occurring in the lower IQ range. The Hayling Sentence Completion Test is a new test, which has been used with success to identify groups of patients with frontal lobe dysfunction (Burgess & Shallice, 1996). The findings of the Hayling Sentence Completion test suggest that the HR subjects, especially those with lower IQs, are poorer at this test of executive function. This is in keeping with previous findings of executive dysfunction in patients with schizophrenia (Elliott & Sahakian, 1995; Elliott *et al.* 1995). We did not find any significant group differences on the other measures of executive function, measures of verbal fluency, or the Stroop test. There was a trend ($P = 0{\cdot}09$) for the control group to achieve faster times on the Stroop than the HR group in the initial analysis. Active cognitive inhibition is required for good performance on both the HSCT and the Stroop. The version of the Stroop that we used was a shortened computerized version of the paper and pencil test, and it became apparent during testing that this test did not prove to be very challenging to the subjects; on the other hand most subjects reported the HSCT to be a challenging task. It could be that subtle difficulties with this aspect of executive function, i.e. cognitive inhibition exists in some members of the HR group in the lower IQ range.

Another interpretation of our findings is that those HR subjects with lower IQs have a general intellectual deficit which impacts on aspects of memory and executive function in a manner different to the analogous normal controls. It

could be that there is a different underlying mechanism in the two groups. Reduced IQ in the individuals with a high genetic risk for schizophrenia was accompanied by deficits in other areas of neuropsychological functioning which was not so marked in normal control subjects. Perhaps this general deficit is inherited as part of the schizophrenic genotype and represents the presence of minimal brain damage as suggested previously (Offord & Cross, 1971) in some subjects at high risk for the development of schizophrenia.

Poor performance on the Hayling Sentence Completion Test was related to family history for schizophrenia. Clearly, the more first-degree relatives affected, the poorer the performance (see Table 6). Similar findings in this sample were found in respect of brain structure, particularly the volume of the third ventricle was significantly increased in the HR subjects with higher genetic loading (Lawrie *et al.* 1999).

We found no differences between the groups in terms of sustained attention, unlike other high risk studies (Rutschmann *et al.* 1977; Nuechterlein, 1983; Cornblatt & Erlenmeyer-Kimling, 1985). The difference between the cited studies and ours being that they were conducted on young children at risk for schizophrenia whereas our HR group are young adults. Cornblatt & Erlenmeyer-Kimling (1984) reported no differences between HR and control subjects on a high demand CPT task in subjects between 13 and 18. Within their sample they reported poorer performance on the task for the 13–14-year-old HR subjects when compared with same age normal controls. The authors interpreted the absence of group differences to reflect age ceiling effects on the CPT.

Faraone *et al.* (1995) reported no differences between relatives of schizophrenic patients and controls on a measure of auditory CPT when both groups were in their mid 30s. In our sample all subjects, both HR and control, commented on the difficulty of the task and we did not find ceiling effects. It may be that sustained attention improves with age and that in the absence of any clinical features or prodromal features of psychosis, there is no evidence for deficits in sustained attention in young adult HR subjects compared with normal controls.

It was noted through the course of testing and analysis that some of the tests proved to be fairly unchallenging to the subjects, particularly the Token Test, and our computerized version of the Stroop, suggesting that these tests may not be sensitive enough to distinguish true differences between the groups in their respective domains of function. In November 1997, nine subjects had psychotic symptoms on Present State Examination (Symptoms 49–92; Wing *et al.* 1974), fully held in four cases, partially held in a further five cases. These findings are very preliminary but at present our interpretation is that certain behavioural and psychopathological characteristics described elsewhere (Hodges *et al.* 1999; Johnstone, 1998) may predict the development of the psychosis while poor performance on some executive and memory tests, set against a background of lower IQ scores and structural abnormalities (Lawrie *et al.* 1999) may indicate inheritance of the genotype.

This study was supported by a Programme Grant from the Medical Research Council. It was conducted with the approval of the Ethics Committees of the areas of Scotland from which the subjects were recruited. Thanks are due to the many GPs and psychiatrists who gave us access to their patients and in particular to the subjects and their extended families for their generous assistance. The neuropsychological assessment battery was designed by the help of Professor Chris Frith and with additional advice from Dr Ronan O'Carroll.

REFERENCES

Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983). Statistical guidelines for contributors to medical journals. *British Medical Journal* **286**, 1289–1493.

Annett, M. (1970). A classification of hand preference by association analysis. *British Journal of Psychology* **61**, 303–321.

Asarnow, J. R. (1988). Children at risk for schizophrenia: converging lines of evidence. *Schizophrenia Bulletin* **14**, 613–631.

Bilder, R. M. (1996). Neuropsychology and neurophysiology in schizophrenia. *Current Opinion in Psychiatry* **9** 57–62.

Burgess, P. W. & Shallice, T. (1996). Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia* **34**, 263–272.

Conover, W. J. & Iman, R. L. (1982). Analysis of covariance using rank transformation. *Biometrics* **38**, 717–724.

Cornblatt, B. & Erlenmeyer-Kimling, L. (1984). Early attentional predictors of adolescent behavioural disturbances in children at risk for schizophrenia. In *Children at Risk for Schizophrenia* (ed. N. F. Watt, E. J. Anthony, L. C. Wynne and J. E. Rolf), pp. 189–211. Cambridge University Press: Cambridge.

Cornblatt, B. & Erlenmeyer-Kimling, L. (1985). Global attentional deviance as a marker of risk for schizophrenia: specificity and predictive validity. *Journal of Abnormal Psychology* **94**, 470–486.

Cornblatt, B. & Obuchowski, N. (1997). Update of high-risk research: 1987–1997. *International Review of Psychiatry* **9**, 437–447.

Cornblatt, B. A., Risch, N. J., Faris, G., Friedman, D. & Erlenmeyer-Kimling, L. (1988). The continuous performance test, identical

pairs version (CPT–IP): I. New findings about sustained attention in normal families. *Psychiatry Research* **26**, 223–238.

Done, D. J., Crow, T. J., Johnstone, E. C. & Sacker, A. (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment of ages 7 and 11. *British Medical Journal* **309**, 699–703.

Elliott, R. & Sahakian, B. J. (1995). The neuropsychology of schizophrenia: relations with clinical and neurobiological dimensions. *Psychological Medicine* **25**, 581–594.

Elliott, R., McKenna, P. J., Robbins, T. W. & Sahakian, B. J. (1995). Neuropsychological evidence for frontostriatal dysfunction in schizophrenia. *Psychological Medicine* **25**, 619–630.

Erlenmeyer-Kimling, L. & Cornblatt, B. (1987). High-risk research in schizophrenia: a summary of what has been learned. *Journal of Psychiatric Research* **21**, 401–411.

Erlenmeyer-Kimling, L., Kestenbaum, C., Bird, H. & Hilldoff, V. (1984). Assessment of the New York High Risk Project subjects in Sample A who are now clinically deviant. In *Children at Risk for Schizophrenia* (ed. N. F. Watt, E. J. Anthony, L. C. Wynne and J. E. Rolf), pp. 227–239. Cambridge University Press: Cambridge.

Faraone, S. V., Seidman, L. J., Kremen, W. S., Pepple, J. R., Lyons, M. J. & Tsuang, M. T. (1995). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. *Journal of Abnormal Psychology* **104**, 286–304.

Fish, B., Marcus, J., Hans, S. L., Auerbach, J. G. & Perdue, S. (1992). Infants at risk for schizophrenia: sequelae of genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem Infant Development Study. *Archives of General Psychiatry* **49**, 221–235.

Golden, C. J. (1978). *Stroop Color and Word Test*. Stoelting: Chicago, IL.

Gottesman, I. I. & Shields, J. (1976). A critical review of recent adoption, twin and family studies of schizophrenia: behavioural genetics perspectives. *Schizophrenia Bulletin* **2**, 360–401.

Gottesman, I. I. & Shields, J. (1982). *Schizophrenia: The Epigenetic Puzzle*. Cambridge University Press: New York.

Gur, R. C., Ragland, D. & Gur, R. E. (1997). Cognitive changes in schizophrenia – a critical look. *International Review of Psychiatry* **9**, 449–457.

Häfner, H. & An Der Heiden, W. (1997). The epidemiology of schizophrenia. *Canadian Journal of Psychiatry* **42**, 139–151.

Heinrichs, R. W. & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* **12**, 426–445.

Hodges, A., Byrne, M., Grant, E. & Johnstone, E. C. (1999). Subjects at risk of schizophrenia – sample characteristics of the first 100 cases in the Edinburgh High Risk Study. *British Journal of Psychiatry* **174**, 547–553.

Johnstone, E. C. (1998). Predictive symptomatology, course and outcome in first-episode schizophrenia. *International Clinical Psychopharmacology* **13** (suppl. 1), 597–599.

Jones, P., Rodgers, B., Murray, R. & Marmot, M. (1994). Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* **344**, 1398–1402.

Kremen, W. S., Seidman, L. J., Faraone, S. V., Pepple, J. R. & Tsuang, M. T. (1992). Attention/information-processing factors in psychotic disorders: replication and extension of recent neuropsychological findings. *Journal of Nervous and Mental Disease* **180**, 89–93.

Kremen, W. S., Seidman, L. J., Pepple, J. R., Lyons, M. J., Tsuang, M. T. & Faraone, S. V. (1994). Neuropsychological risk indicators for schizophrenia: a review of family studies. *Schizophrenia Bulletin* **20**, 103–119.

Kremen, W. S., Goldstein, J. M., Seidman, L. J., Toomey, R., Lyons, M. J., Tsuang, M. T. & Faraone, S. V. (1997). Sex differences in neuropsychological function in non-psychotic relatives of schizophrenic probands. *Psychiatry Research* **66**, 131–144.

Lawrie, S. M., Whalley, H., Kestelman, J. N., Abukmeil, S. S., Byrne, M., Hodges, A., Rimmington, J. E., Best, J. J. K., Owens, D. C. G. & Johnstone, E. C. (1999). Magnetic resonance imaging of the brain in subjects at high risk of developing schizophrenia. *Lancet* **353**, 30–33.

Lewine, R., Haden, C., Caudle, J. & Shurett, R. (1997). Sex-onset effects on neuropsychological function in schizophrenia. *Schizophrenia Bulletin* **23**, 51–61.

Lezak, M. D. (1995). *Neuropsychological Assessment, 3rd edn*. Oxford University Press: New York.

Neale, J. M., Winters, K. C. & Weintraub, S. (1984). Information processing deficits in children at high risk for schizophrenia. In *Children at Risk for Schizophrenia* (ed. N. F. Watt, E. J. Anthony, L. C. Wynne and J. E. Rolf), pp. 264–278. Cambridge University Press: Cambridge.

Nelson, H. E. (1982). *The National Adult Reading Test (NART): Test Manual*. NFER-Nelson: Windsor, Berks.

Nelson, H. E. & O'Connell, A. (1978). Dementia: the estimation of premorbid intelligence levels using the National Adult Reading Test. *Cortex* **14**, 234–244.

Nuechterlein, K. H. (1983). Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. *Journal of Abnormal Psychology* **94**, 4–28.

Offord, D. R. & Cross, L. A. (1971). Adult schizophrenia with scholastic failure or low IQ in childhood. *Archives of General Psychiatry* **24**, 431–436.

Oldfield, B. C. (1971). The assessment and analysis of the Edinburgh Inventory. *Neuropsychologica* **9**, 97–113.

Ott, S. L., Spinelli, S., Rock, D., Roberts, S., Amminger, G. P. & Erlenmeyer-Kimling, L. (1997). The New York High Risk project; social and general intelligence in children at risk for schizophrenia. *Schizophrenia Research* **31**, 1–11.

Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *British Medical Journal* **316**, 1236–1238.

Rey, A. (1964). *L'examen clinique en psychologie*. Presses Universitaires de France: Paris.

Rutschmann, J., Cornblatt, B. & Erlenmeyer-Kimling, L. (1977). Sustained attention in children at risk for schizophrenia: report on a Continuous Performance Test. *Archives of General Psychiatry* **34**, 571–575.

Spreen, O. & Benton, A. L. (1969). *Neurosensory Centre Comprehensive Examination for Aphasis (NCCEA)*. Neuropsychological Laboratory, University of Victoria: Victoria, Australia.

Spreen, O. & Benton, A. L. (1977). *Neurosensory Centre Comprehensive Examination for Aphasis (NCCEA) (revised edn)*. Neuropsychological Laboratory, University of Victoria, Victoria, Australia.

Spreen, O. & Strauss, E. (1991). *A Compendium of Neuropsychological Tests*. Oxford University Press: New York.

SPSS (1996). *SPSS 7·5 for Windows*. SPSS Inc.: Chicago.

Toomey, R., Faroane, S. V., Seidman, L. J., Kreman, W. S., Pepple, J. R. & Tsuang, M. T. (1998). Association of neuropsychological vulnerability markers in relatives of schizophrenic patients. *Schizophrenia Research* **31**, 89–98.

Walker, E. F., Savoie, T. & Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophrenia Bulletin* **20**, 441–451.

Walker, E. F., Grimes, K. E., Davis, D. M. & Smith, A. J. (1993). Childhood precursors of schizophrenia: facial expressions of emotion. *American Journal of Psychiatry* **150**, 1654–60.

Wechsler, D. (1981). *WAIS-R Manual*. Psychological Corporation: New York.

Wechsler, D. (1987). *Wechsler Memory Scale – Revised Manual*. The Psychological Corporation: San Antonio, TX.

Weinberger, D. R. (1995). From neuropathology to neurodevelopment. *Lancet* **346**, 552–557.

Wilson, B. A., Cockburn, J. & Baddeley, A. (1985). *The Rivermead Behavioural Memory Test*. Thames Valley Test Co.: Reading.

Wing, T. K., Cooper, J. E. & Sartorius, N. (1974). *Measurement and Classification of Psychiatric Symptoms: An Instruction Manual for the PSE and CATEGO Program*. Cambridge University Press: London.